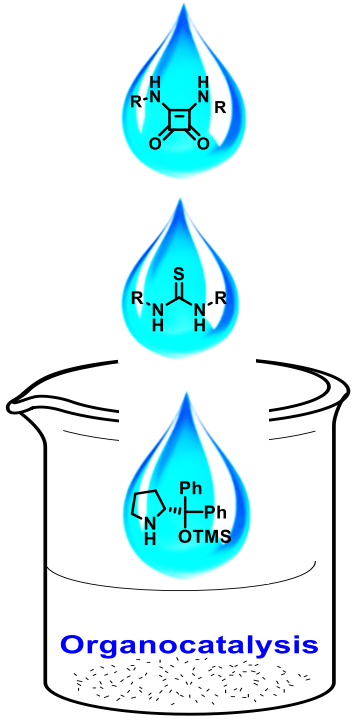
From Monofunctional to Unconventional Bifunctional Organocatalytic Systems



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A Kas, mi casualidad más bonita

ABBREVIATIONS[1]

ABH aza-Baylis-Hillman

Ac: Acetyl

Aq. Aqueous

Ar: Aryl

App. Appearance

Bn: Benzyl

Boc: *tert*-Butoxycarbonyl

bs: Broad single

ºC

Cat Catalyst

CDDP *cis*-platin

δ Chemical shift

DABCO 1,4-diazabiclyclo[2.2.2.]octane

DBU: 1,8-Diazabiciclo[5.4.0]undec-7-eno

DCE: 1,2-Dicloroethane

DCM Dichloromethane

DFT Density functional theory

Dr Diasteromeric ratio

E^+: Electrophile

ee: Enantiomeric excess

Eq. Equivalent

Et Ethyl

et al. Et alii (and others)

ES: Electrospray

EWG: Electron-withdrawing group

[1] For standard abbreviations and Acronyms, see: "Guidelines for Authors" J. Org. Chem. 2017.

Het	Heteroatom
HOMO	Highest occupied molecular orbital
HPLC:	High Performance liquid chromatography
HRMS	High Resolution mass spectroscopy
Hz	Hertz
IE:	Electronic Impact
J	Coupling constant
LDA:	Lithium diisopropyamide
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
M^+	Molecular ion
Me	Methyl
n.d	Not determined
n.O.e	Nuclear Overhauser effect
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect correlation spectroscopy
Nu	Nucleophile
o	ortho
p	para
Ph	phenyl
Ppm	Parts per million
i-Pr	Isopropyl
q	quartet
rt	room temperature
rac	racemic
RC	Rauhut-Currier
s	singlet
sat.	Aqueous saturated solution

SFC	Supercritical fluid cromatography
t	triplet or time
T	Temperature
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
THF	Tetrahydrofuran
TLC	Thin-layer cromatography
T_{major}	Retention time of the major enantiomer
T_{minor}	Retention time of the minor enantiomer
TMS	Trimethylsilyl
Ts	Tosyl
X	Halogen

RESUMEN

El trabajo de investigación presentado en esta tesis doctoral, se centra en el área de la Organocatálisis y consta de cuatro capítulos. A lo largo de estos capítulos, diferentes metodologías organocatalíticas enantioselectivas han sido desarrolladas, con el fin de obtener compuestos orgánicos de interés farmacéutico e industrial.

Cada uno de los cuatro capítulos de esta tesis presentan enumeración independiente, de forma que los productos nuevos obtenidos en esta tesis vienen asignados con números latinos, los compuestos procedentes de la bibliografía con letras y los intermedios de reacción con números romanos.

En el primer capítulo, a través de la aminocatálisis, hemos podido describir una reacción "one pot" para la síntesis enantioselectiva de 2,3-diheteroarilalcanales, de tremenda importancia como productos naturales. Además, se ha podido estudiar también su actividad antitumoral.

En el capítulo dos, se ha llevado a cabo una revisión bibliográfica sobre la reacción de Mukaiyama viniloga. Se ponen de manifiesto los distintos modos de activación existentes así como las ventajas y limitaciones de cada método.

En el capítulo tres, hemos demostrado que en presencia de catalizadores bifuncionales es posible cambiar la regioselectividad de silil-dienol éteres de 1,5 a la funcionalización 1,3. Este hecho ha permitido el acceso a una gran variedad de productos tipo Rauhut-Currier, con buenos rendimientos y altos excesos enantiomericos.

Por último en el capítulo cuatro, hemos querido expandir la metodología expuesta en el capítulo anterior, pero esta vez empleando iminas como electrófilos, lo que nos ha permitido describir un método general para la síntesis enantioselectiva de productos tipo aza-Baylis-Hillman, alguno de ellos muy difíciles de obtener por métodos convencionales.

ABSTRACT

The work compiled in this doctoral thesis is focused on Organocatalysis and contains four chapters. Along these chapters, different asymmetric and organocatalytic methodologies have been developed, in order to obtain organic compounds with valuable pharmaceutical and industrial properties.

Each of the four chapters of this thesis presents independent enumeration. The new products obtained in this PhD. have been assigned with latins numbers, the compounds described in the literature with letters and the reaction intermediates with romans numbers.

In the first chapter, we have developed a methodology for the synthesis of enantioenriched 2,3-diheteroarylalkanals employing aminocatalysis. The desired products have tremendous importance as natural products. We have also carried out the antiproliferative analysis of the new compounds.

In chapter two, a review of the Vinylogous Mukaiyama is presented. It is shown all the different modes of activation of this reaction as well as all the advantages and drawbacks of every method described.

In chapter three, we have shown that in the presence of a bifunctional catalysts it is possible to change the regioselectivity of the silyl-dienol ethers from 1,5 to the 1,3 functionalization.. This fact makes possible the access to a wide range of Rauhut-Currier type-products, with good yields and excellent enantioselectivities.

In the last chapter, we have expanded the methodology described in the previous chapter, but in this case employing imines as the electrophile, obtaining a general method for the enantioselective synthesis of aza-Baylis-Hillman type-products, which most of them are difficult to achieve by other convenctional methods.

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CHAPTER 1

Dienamine and Friedel-Crafts Reaction One pot Synthesis and Antitumor Evaluation of Diheteroarylalkanals

1.1. Introduction to the Organocatalysis

In the past decade, organocatalysis has emerged as a powerful and environmentally benign strategy towards numerous organic transformations.[1] Since its renaissance it has been proven to be a robust and useful tool, and equally as competent as metal or enzyme catalysis.

Organocatalysts have two main functions, they can activate the electrophile or the nucleophile (or both of them in the case of bifunctional catalysis), or they can create an assymetric environment that is responsible for setting the chirality of the product. Organocatalysts can be classified by mode of action as covalent or non-covalent (Figure 1). In covalent catalysis, a covalent bond between the organocatalyst and the substrate is formed, increasing the interaction between the substrate and the reagent in the reaction. Amines or carbenes are included in this section. However, in non-covalent catalysis, the activation of the substrate goes through a hydrogen bond (thioureas, squaramides) or ionic interactions (chiral bases).

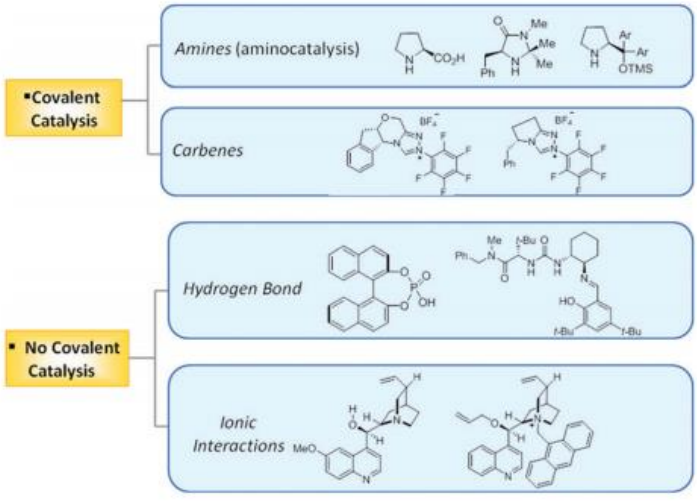
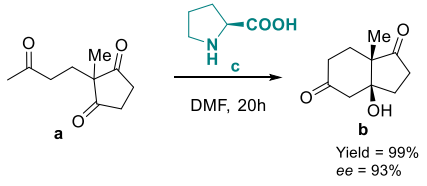


Figure 1. Different mode of action of organocatalysts.

[1] a) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed*, **2001**, *40*, 3726. b) D.W.C Macmillan, *Nature*, **2008**, *455*, 304. c) P. Melchiorre, Angew. Chem. Int. Ed. **2009**, *48*, 1360. d) C. M. Marson, Chem. Rev. 2012, 41, 7712. e) J. Wang, B. List, *Science*, **2006**, 1584. f) K. A. Ahrendt, C. J., D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243. g) E. N. Jacobsen, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA*, **2010**, *107*, 20618. h) J. L. Vicario, D. Badia, L. Carrillo, E. Reyes, RSC publishing: Cambridge, 2010. i) B. List, *Chem. Rev*, **2007**, *107*, 5413. j) Y. Quin, L. Zhu, S. Luo, *Chem. Rev.* **2017**, *117*, 9433. k) P. Vogel, Y. Lam, A. Simon, K. Houk, *Catalysts*, **2016**, *6*, 128.

In 2000, the concepts of LUMO[2]-lowering (iminium ion) and HOMO-raising (α-functionalisation *via* enamine[3]) organocatalytic strategies, were applied to the activation of both, unsaturated and saturated, carbonyl compounds. Since then, the application of asymmetric aminocatalysis to activate a more remote position has been under consideration, but it has taken several years for it to be accomplished (in contrast to the remarkably quick advances in the field of the chiral auxiliaries).[4] From a historical point of view, the stoichiometric enamine preparation was first made practical by Mannich and Davidsen and it was used for the first time, in a catalytic manner, in the well-known Hajos-Parrish-Ender-Sauer-Wiechert reaction (Scheme 1).[5]



Scheme 1. The Hajos–Parrish–Eder–Sauer–Wiechert reaction.

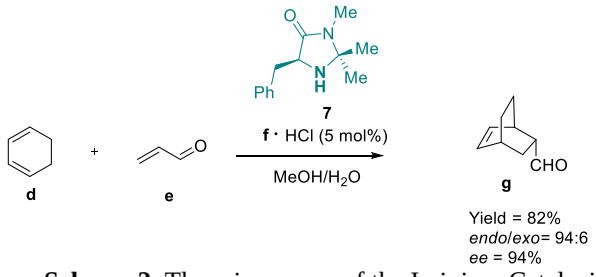
In the present chapter, two main aminocatalysis strategies will be used, and in the next section, the most important features of iminium ion and dienamine catalysis will be described.

1.2. Iminium Ion catalysis

In 2000, MacMillan and coworkers reported the first asymmetric Diels Alder reaction under aminocatalysis influence. In this work, a new suitable imidazolidinone catalyst (**f**) was described to promote the activation of α,β-unsaturated aldehydes

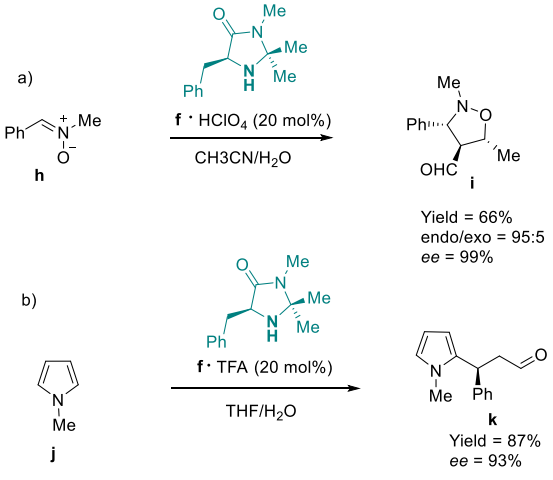
[2] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc*, **2000**, *122*, 4243.
[3] Reviews on enamine catalysis: a) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res*, **2004**, *37*, 580. b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev*, **2007**, *107*, 5471.
[4] (a) M. C. Whisler, S. MacNeil, V. Snieckus and P. Beak. *Angew. Chem. Int. Ed.* 2004, **43**, 2206; (b) K. Mikami, M. Shimizu. H.-C. Zhang and B. E. Maryanoff, *Tetrahedron* 2001, **57**, 2917.
[5] U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed*, **1971**, *10*, 496.

(Scheme 2).[6] With this example, a new catalytic activation concept emerged: **the Iminium Catalysis.** This catalysis is based on covalent active intermediates, which are a result of the reversible condensation of chiral cyclic amines with a carbonyl group, leading to an iminium ion intermediate, which allows the β and α-functionalization of the aldehyde.



Scheme 2. The reinassance of the Iminium Catalysis.

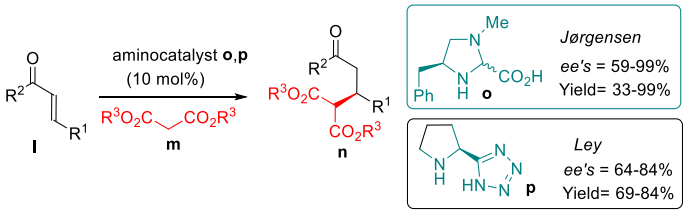
One year later, the same research also developed the organocatalytic 1,3-dipolar[7] and Friedel-Crafts[8] reactions (Scheme 3). Both examples afforded the corresponding products with good results in terms of enantioselectivities (93-99% *ee*) and yields (Scheme 4).



Scheme 3. Enantioselective 1,3-dipolar addition and Friedel- Crafts reactions.

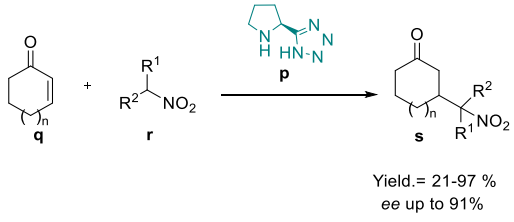
[6] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem.Soc*. **2000**, *122*, 4243.
[7] W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2000**, *122*, 9874.
[8] N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc*, **2001**, *123*, 4370.

In 2003, Jorgensen and Ley's groups independently, published the Michael addition of malonates to acyclic enones under the influence of phenylalanine and imidazole derived catalysts, respectively (Scheme 4).[9]



Scheme 4. Michael addition of malonates to enones.

One of the most studied reactions is the addition of nitroalkenes to different enones and α,β-unsaturated aldehydes. For example in the Scheme 5, it is shown the methodology described by Ley and co-workers.[10] They employed the tetrazol derived **p** from proline as the best catalyst to promote the addition of nitroalkanes to cyclohexenones in high enantioselectivities.



Scheme 5. Addition of nitroalkanes to cyclohexenones.

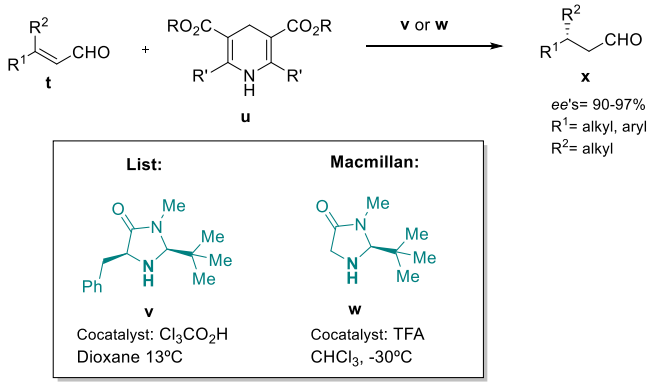
Since the presentation of this novel assymetric strategy, many research groups have focused their attention in the introduction of different nucleophiles of H, S, N and O. For example, MacMillan and List's groups published the enantioselective reduction of enals under iminum catalysis, employing Hantzsch dihydropyridines as hydride

[9] a) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem. Int. Ed*. **2003**, *42*, 661. b) K. R. Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Commun*. **2006**, 66.

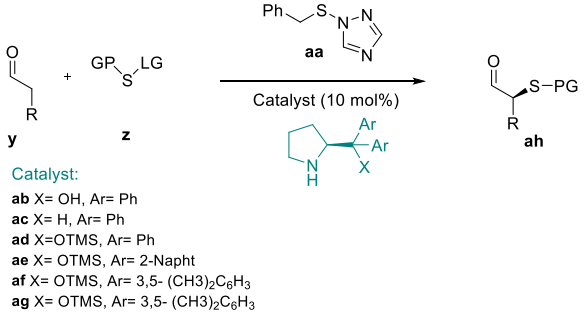
[10] C. E. T. Mitchell, S. E. Brenner, J. Garcia-Fortanet, S.V. Ley, *Org. Biomol. Chem*. **2006**, *4*, 2039.

donors.[11] Surprisingly, List's group used imidizolidinone **v** as the catalyst, while Macmillan group employed the new aminocatalyts **w** (Scheme 6).

On the other hand, in 2005 Jørgensen and coworkers reported the first organocatalytic electrophilic α-sulfenylation of aldehydes.[12] The most surprising of this work, apart from the fact of achieving this valuable transformation, was the presentation of a new class of organocatalyst. Starting from the inactive diphenylprolinol **ab** and with a simple protection of the oxygen atom with trimethylsilyl group, led to the catalyst **ad**. Small modifications in the aromatic moieties (aminocatalyst **af)** promotes the formation of the sulfenylated products in high yield and *ee*'s up to 95% (Scheme 7).



Scheme 6. Transfer hydrogenation under iminium catalysis.

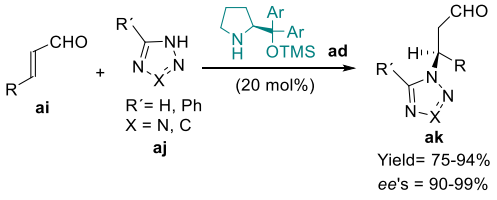


Scheme 7. Enantioselective sulfenylation of aldehydes under aminocatalysis.

[11] a) S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2005**, *127*, 32. b) J. W. Yang, M. T. Hechavarria, N. Vignola, B. List, *Angew. Chem.* **2005**, *117*, 110.

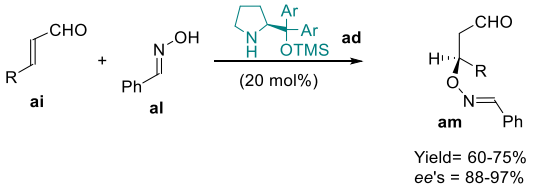
[12] M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed*. **2005**, *44*, 794.

The enantioselective formation of C-N bonds was carried out independently by MacMillan and Cordova's groups, employing trialkylsilyloxycarbamates[13]. By contrast, nitrogen heterocycles were used by Jorgensen and Vicario in order to achieve new chiral centers (Scheme 8).[14]



Scheme 8. Enantioselective formation of C-N bonds.

The oxa-Michael addition to this type of systems was not achieve until 2007, when Jorgensen developed the enantioselective version of this addition in the presence of oximes **al** as the oxygen source (Scheme 9).[15] The reaction took place under smooth conditions and high enantioselectivities (up to 97%).



Scheme 9. Enantioselective oxa-Michael addition.

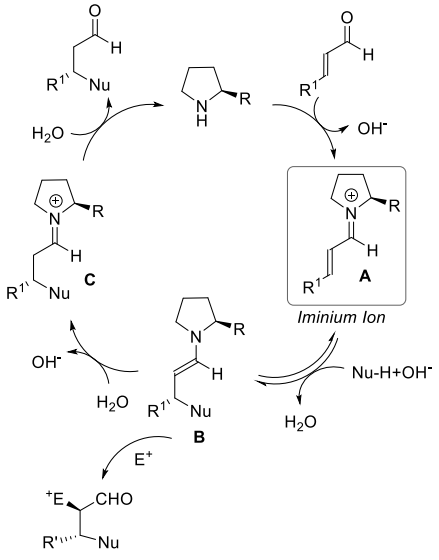
The most accepted mechanistic proposal for the iminium ion activation is shown in Scheme 10. The process starts with the condensation between the aminocatalyst and the α,β-unsaturated aldehyde, resulting on the corresponding iminium ion (**A**). The iminium ion **A** is attacked only by one of its two prochiral faces, the less hindered one. This resulted on the formation of the enamine, which captures a proton from a water molecule (or another electrophile), affording the enantiomerically enriched final

[13] a) Y. K. Chen, M. Yoshida, D. W. C. Macmillan, *J. Am. Chem. Soc*, **2006**, *128*, 9328. b) J. Vesley, I. Ibrahem, R. Rios, G. L. Zhao, Y. Xu, A. Cordoba, *Tetrahedron Lett.* **2007**, *48*, 2193.

[14] a) P. Diner, M. Nielsen, M. Marigo, K. A. Jorgensen, *Angew. Chem. Int. Ed*. **2007**, 46, 1983. b) U. Uria, J. L. Vicario, D. Badia, L. Carrillo, *Chem. Commun*. **2007**, 2509.

[15] S. Bertelsen, P. Diner, R. L. Johansen, K. A. Jorgensen, *J. Am. Chem. Soc*. **2007**, *129*, 1536.

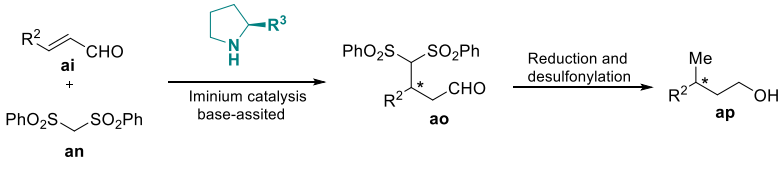
product after the hydrolysis of the iminium ion intermediate. When an electrophile different from a H^+ is used, a tandem reaction with the incorporation of a nucleophile and electrophile can take place (botton-left Scheme 10).



Scheme 10. Mechanistic proposal for the Iminium Ion activation.

1.2.1. Precedents of the group

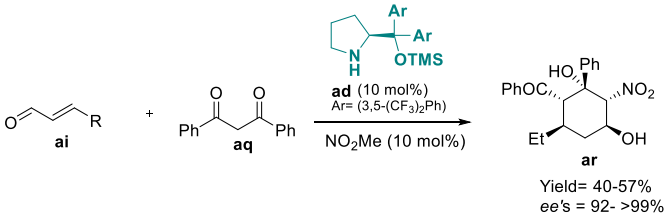
If we have a look in the literature, we can find several examples regarding the experience of my group in the Iminium Ion catalysis. For example in 2009, an indirect organocatalytic method for the β-methylation of α,β-unsaturated aldehydes **ai** was presented. The reaction involves the addition of bis(arylsulfonyl)methane **an** catalyzed by prolinol derivatives and further elimination of the chameleonic sulfonyl groups (Scheme 11).[16]



Scheme 11. Organocatalytic addition of bis(arylsulfonyl)methane to α,β-unsaturated aldehydes.

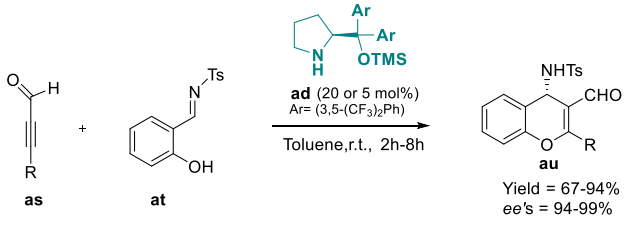
[16] J. L. García Ruano, V. Marcos, J. Alemán, *Chem. Commun*., **2009**, 4435.

In the same year, my group described a one-pot reaction which combines diarylprolinol ether and TBAF results in an effective synthesis of ciclohexanes **ar** with five chiral centers from α,β-unsaturated aldehydes **ai**, β-dicarbonyl compounds **aq**, and nitromethane. The reaction proceeded with high-enantio- and diastereoselectivity for a wide range of substrates (Scheme 12).[17]



Scheme 12. Synthesis of pentasubstituted cyclohexanes.

In 2010, they presented the first highly enantioselective oxa-Michael/aza-Baylis-Hillman tandem reaction between 2-alkynals **aa** and tosylimines **at** leading to optically active 4-amino-4*H*-chromenes (Scheme 13). [18]

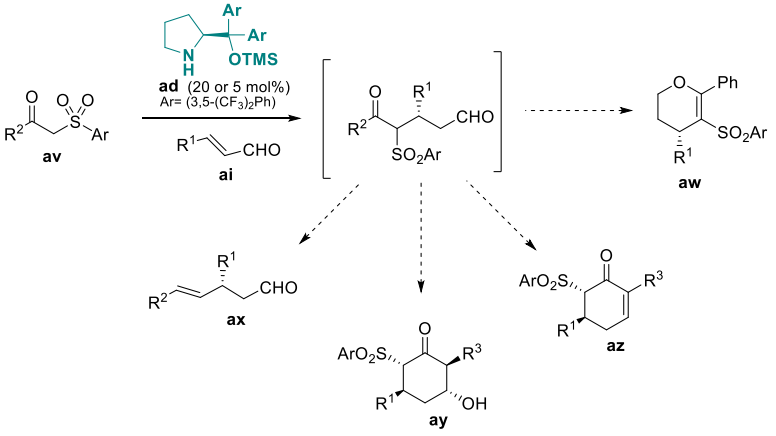


Scheme 13. Approach to the synthesis of 4-aminochromenes.

Also in 2010, my group studied the influence of different reaction conditions on the conjugated addition of β-keto sulfones **av** to α,β-unsaturated aldehydes **ai** catalyzed by silyl prolinol ethers **ad**. They realised that small changes in the starting material or

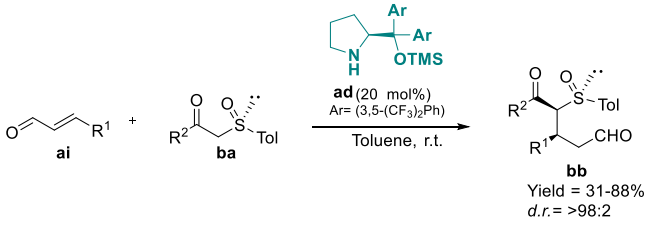
[17] J. L. García Ruano, V. Marcos, J. A. Suanzes, L. Marzo, J. Alemán, *Chem. Eur. J.* **2009**, *15*, 6576.
[18] J. Alemán, A. Nuñez, L. Marzo, V. Marcos, C. Alvarado, J. L. García Ruano, *Chem. Eur. J.* **2010**, *16*, 9453.

in the experimental protocol are able to produce significant variations in the structures of the final products **aw**-**az** (Scheme 14).[19]



Scheme 14. Transformations of the adducts, formed by the addition of β-keto sulfones to α,β-unsaturated aldehydes.

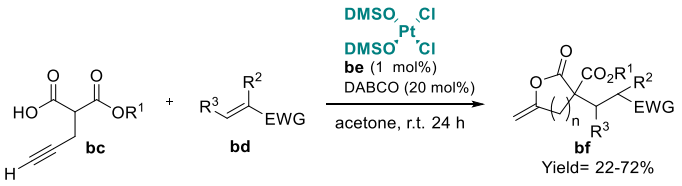
In 2011, they found out that the use of enantiomerically pure β-ketosulfoxides **ba** as nucleophiles in 1,4-additions to α,β-unsaturated aldehydes **ai** catalyzed by proline derivatives **ad** allowed complete control of the two chiral centers to be simultaneously created in the reaction (Scheme 15).[20]



Scheme 15. Organocatalytic addition of β-ketosulfoxides to conjugated aldehydes.

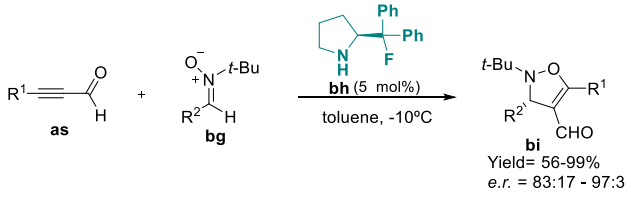
In the same year, my group discovered that the use of a catalytic amount of platinum complexes **be** was compatible with different organocatalysts such as DABCO or the Jorgensen-Hayashi catalyst. These catalysts were used in the functionalization of different activated methylenes. A series of lactones **bf** with C-3 quaternary centers and substitution at C-5 were prepared (Scheme 16). [21]

[19] J. Alemán, V. Marcos, L. Marzo, J. L. García Ruano, *Eur. J. Org. Chem.* **2010**, 4482.
[20] J. L. García Ruano, C. Alvarado, S. Díaz-Tendero, J. Alemán, *Chem. Eur. J.* **2011**, *17*, 4030.
[21] J. Alemán, V. Solar, C. Martín-Santos, L. Cubo, C. Navarro Ranninger, *J. Org. Chem.* **2011**, *76*, 7287.



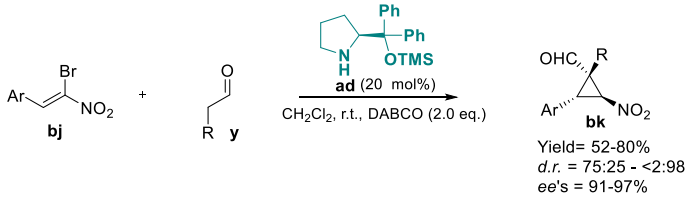
Scheme 16. Tandem Cyclization-Michael Reaction.

In 2012, they published the first organocatalytic enantioselective 1,3-dipolar reaction between nitrones **bg** and alkynals **aa** catalyzed by (*S*)-2-(fluorodiphenylmethyl)pyrrolidine **bh** to give 4-isoxazolines **bl** with high enantiomeric excess and excellent yields (Scheme 17).[22]



Scheme 17. Synthesis of 4-isoxazolines.

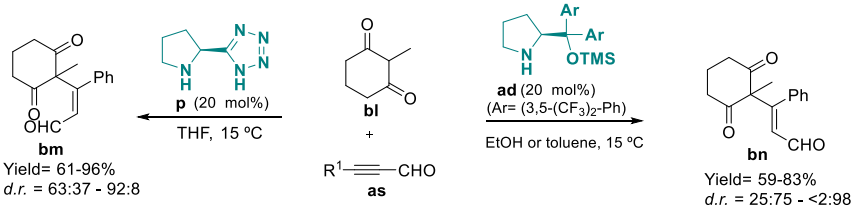
In 2015, my group developed the asymmetric synthesis of cyclopropanes with a quaternary center, using a one pot reaction resulting in excellent enantioselectivities and good yields. The one-pot reaction is based on a first step aminocatalytic reaction between aldehydes **y** and bromonitroalkenes **bj**, followed by a second-step intramolecular bromo substitution catalyzed by DABCO (Scheme 18).[23]



Scheme 18. Asymmetric synthesis of cyclopropanes.

[22] J. Alemán, A. Fraile, L. Marzo, J. L. García Ruano, C. Izquierdo, S. Díaz-Tendero, *Adv. Synth. Catal*. **2012**, *354*, 1665.
[23] J. Luis-Barrera, R. Más-Ballesté, J. Alemán, *ChemPlusChem*, **2015**, *80*, 1595.

In 2016, they presented a highly diastereoselective synthesis of trisubstituted *Z* or *E* enals (**bm** and **bn**) by using different alkynals **aa** and nucleophiles **bl** as starting materials. The diastereocontrol is mainly governed by the catalyst used. Thus, the reactions controlled by steric effects, like Jorgensen-Hayashi's catalyst, give access to *E* isomers through thermodynamic control, whereas catalyst such as tetrazol-pyrrolidine Ley's catalyst allow the synthesis of *Z* isomers, obtained by means of kinetic control (Scheme 19).[24]



Scheme 19. Diastereo-divergency for alkynals through aminocatalysis.

1.3. Dienamine Catalysis

The need of scientists to functionalize remote positions far away from the catalyst activation site led to the birth of dienamine[25] and trienamine chemistry.[26] In the case of the dienamine, the γ functionalization can take place with high enantioselectivities. In the next pages, we will summarize the main achievements in the γ functionalization through the dienamine catalysis (Figure 2).

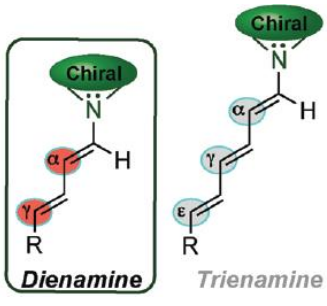


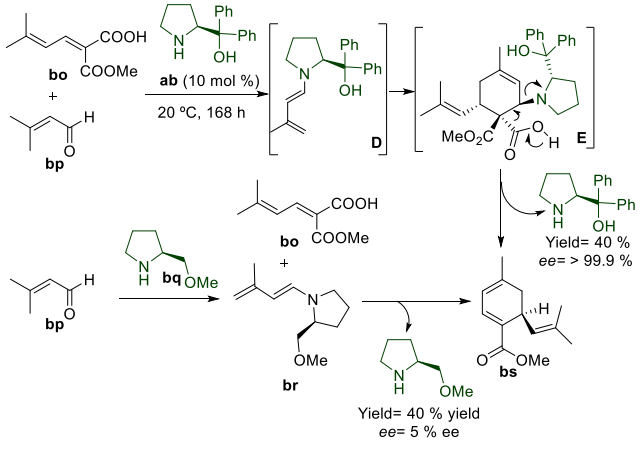
Figure 2. Different functionalisation of aldehydes.

[24] L. Marzo, J. Luis-Barrera, R. Mas-Ballesté, J. L. García Ruano, J. Alemán, *Chem. Eur. J.* **2016**, *22*, 16467.

[25] a) V. Marcos, J. Alemán, Chem. Soc. Rev. 2016, 45, 6812. b) A. Fraile, J. Alemán, Synlett. 2015, 26, 1940. c) D. Ramachary, Y. Reddy, *Eur. J. Org. Chem.* **2012**, *5*, 865.

[26] a) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2003**, *42*, 4233. b) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Synlett*, **2003**, 1910. c) S. Reboredo, A. Parra, J. Alemán, *Asymm. Catal.* **2014**, *1*, 24. d) I. Kumar, P. Ramaraju, N. Mir, *Org. Biomol. Chem.* **2013**, *11*, 709.

In 1993 Serebryakov and colleagues were the first to study the stoichiometric and organocatalytic dienamine activation of α,β-unsaturated aldehydes (Scheme 12).[27] In these works, the authors described the synthesis of different polysubstituted cyclohexadienes, using the HOMO-raising activation of the dienamine system. The authors reported that after the formation of the chiral dienamine, a subsequent cycloaddition from its sterically less hindered face to a dienophile (*exo* or *endo* approach) can take place to give the final cycloadducts which, after hydrolysis and release of the catalyst, could give the polysubstituted cyclohexadienes. This mechanism was supported experimentally through the isolation of different chiral dienamine intermediates by condensation of an aldehyde with a chiral secondary amine and subsequently reacting these dienamines with the dienophile in a two-step process (see bottom, Scheme 20).



Scheme 20. First organocatalytic dienamine activation.

There are different reactivity pathways of dienamine[28] as we can find in Figure 3. However, in this introduction we are only going to focus on the 1,5-reactivity because it is the one involved with this chapter.

[27] A. G. Nigmatov, E.P. Serebryakov, *Russ. Chem. Bull*, **1993**, *42*, 213.
[28] a) S. H. Chen, B. C. Hong, C. F. Su, S. Sarshar, *Tetrahedron Lett*, **2005**, *46*, 1878. b) B. C. Hong, H.C. Tseng, S. H. Chen, *Tetrahedron*, **2007**, *63*, 2840. c) J. L. Li, T. R. Kang, S. L. Zhou, R. Li, L. Wu, Y. C. Chen, Angew. Chem. Int. Ed, 2010, 49, 6418. d) L. Albrecht, G. Dickmeiss, F. Cruz Acosta, R. L. Davis, K. A. Jørgensen, *J. Am. Chem. Soc*, **2012**, *134*, 2543.

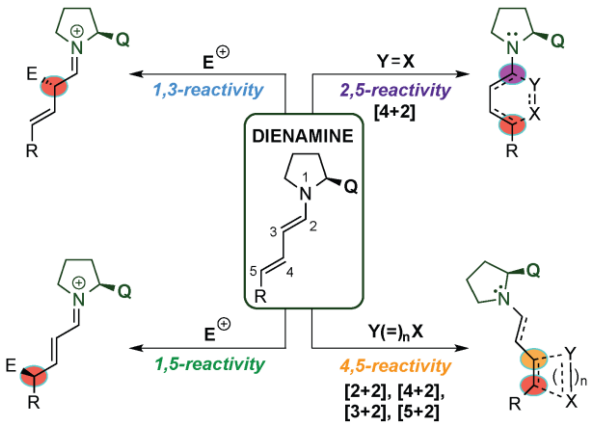


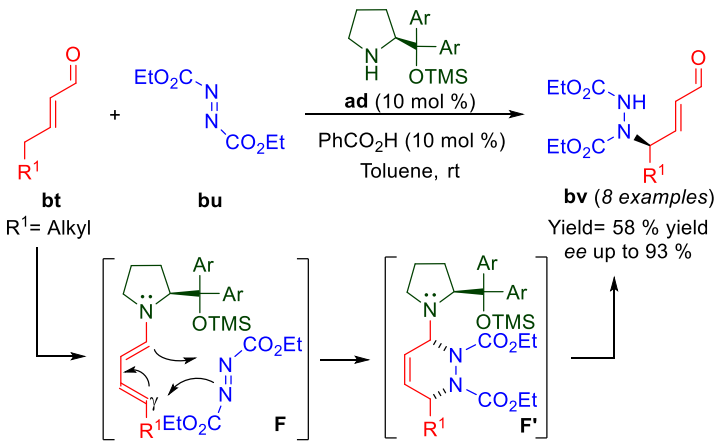
Figure 3. Different reactivity pathways of dienamine.

1.3.1. 1,5-Reactivity: γ-remote functionalisation

In 2006, Jørgensen and co-workers reported the first example of an asymmetric vinylogous catalytic process through dienamine activation of γ-enolisable unsaturated aldehydes (top, Scheme 21).[29] They developed the γ-amination of different α,β-unsaturated aldehydes (**bt**) with diethyl azodicarboxylate (**bu**) under aminocatalysis using **ad** with moderate yields and high enantioselectivities and perfect site selectivity for the γ position. To support the excellent stereo- and selectivity observed in the reaction, the authors reported experimental and theoretical studies that suggested a [4+2] cycloaddition path as the most probable reaction mechanism of the reaction.

In this concerted mechanism under this reaction conditions, the generated hetero-Diels-Alder adduct **F'** evolves to the final product **bv** and the concerted transition state **F** proceed via a dienamine *E,s-cis, E*, which is support by the experimental stereochemical outcome obtained in the reaction (Scheme 21).

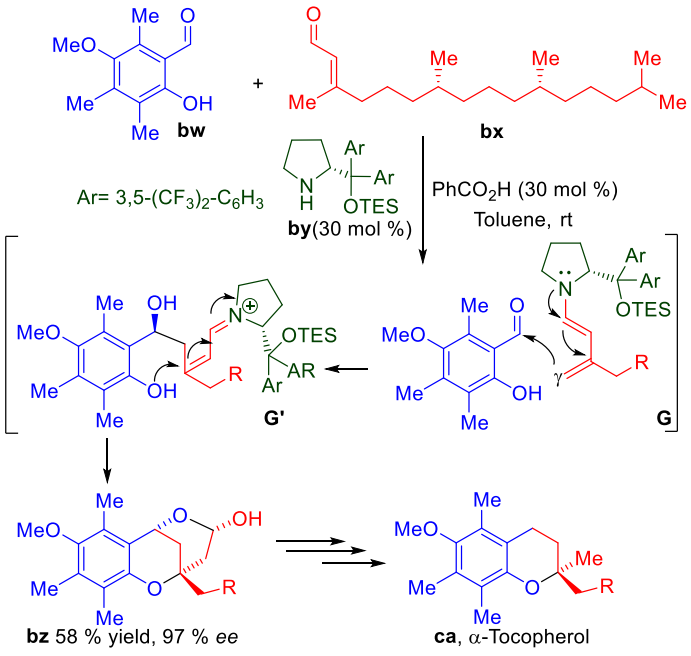
[29] S. Bertelsen, M. Marigo, S. Brandes, P. Diner, K. A. Jorgensen, *J. Am. Chem. Soc*, **2006**, *128*, 12973.



Scheme 21. Asymmetric vinylogous γ-amination of α,β-unsaturated aldehydes.

This seminal work reported by Jørgensen´s group inspired other groups to explore the potential of dienamine activation as a powerful tool for the direct asymmetric 1,5-functionalisation of *α,β*-unsaturated aldehydes. In 2008, Woggon and colleagues reported an aldol/oxa-Michael cascade process *via* dienamine-iminium ion intermediates (**G, G'**), as a key step in the total synthesis of *α*-Tocopherol (**ca**) a member of the E vitamin family (Scheme 14).[30] The product obtained via the cascade sequence is submitted to a three step synthetic process based on ring opening *via* hydrogenation, decarboxylation and demethylation leading to the target molecule **az** (botton Scheme 22). The dienamine catalysed reaction proceeded with a perfect *γ*-regioselectivity and can be considered an astonish demonstration of the potential of the dienamine activation as a tool in the total synthesis of natural products.

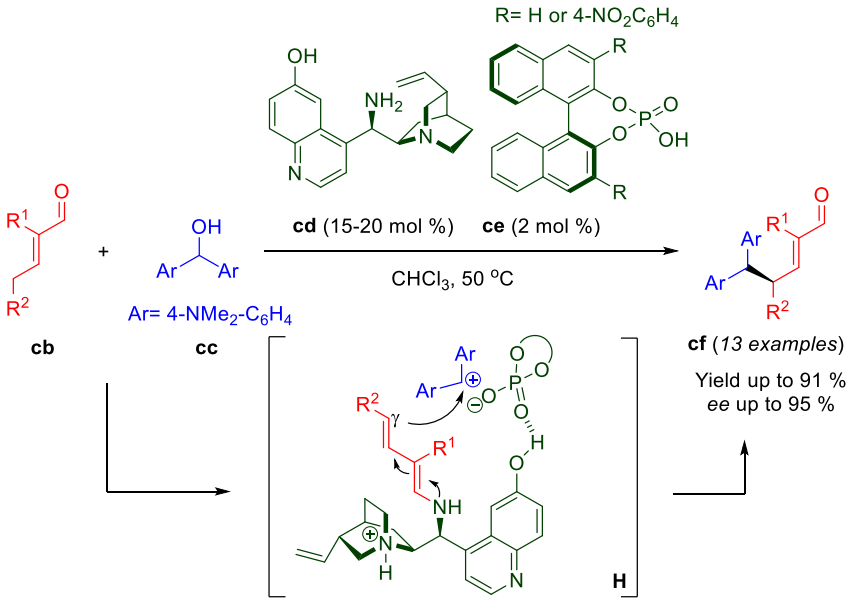
[30] K. Liu, A. Chougnet, W. D. Woggon, *Angew. Chem. Int. Ed*, **2008**, *47*, 5287.



Scheme 22. Total synthesis of tocopherol

Targeting to develop discrete intermolecular nucleophilic additions of the remote γ-position of enals, concurrently and independently to Christmann's work ,[31] Melchiorre's group developed a cooperative catalytic system based on a combination of chiral primary amine **cd** and chiral phosphoric acid **ce** able to promote the *γ*-site-selective alkylation of *α*-branched enals **cb** *via* an S_N1 pathway (Scheme 23). The authors proposed that the reaction between *α*-branched enals and bis[4-(dimethylaminophenyl)methanol (**cc**) proceeds through a cooperative activation path that combines dienamine- and Brønsted-acid activation modes simultaneously. In the transition states (**H**), **ce** participate in the formation of a chiral contact ion pair with **cc**, which react with the chiral dienamine intermediate generated from condensation with **cb**. Thus, through an interwoven of non-covalent interaction of the cooperative catalytic system and the reagents, the reaction furnishes exclusively **cf** with excellent yields and enantioselectivities.

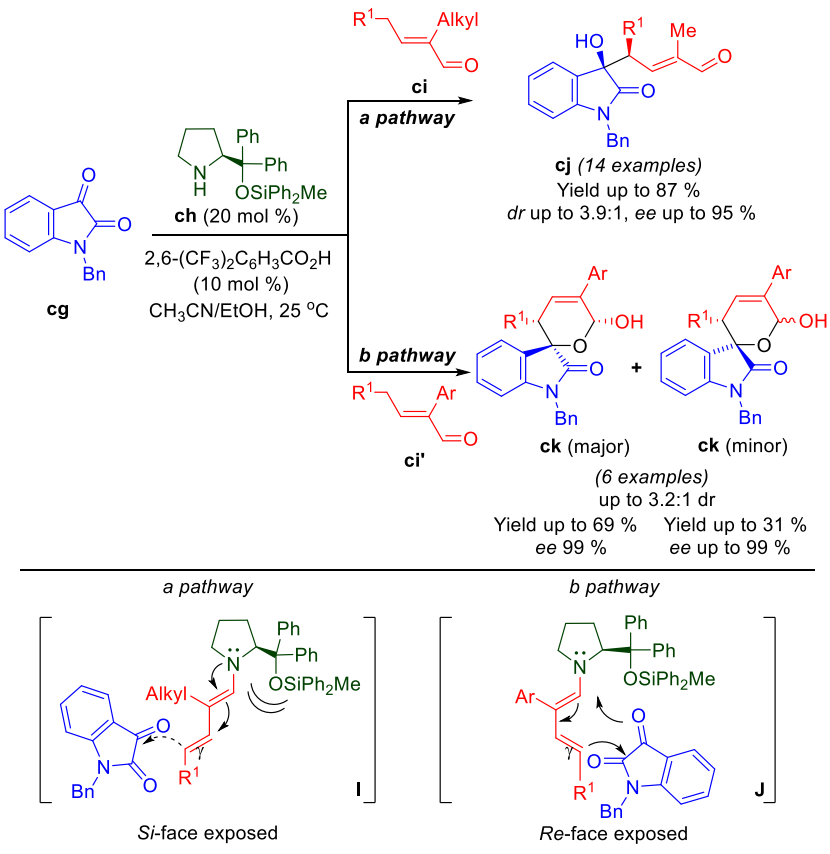
[31] J. Stiller, E. Marques-Lopez, R. P. Herrera, R. Frohlich, C. Strohmann, M. Christmann, *Org. Lett*, **2011**, *13*, 70.



Scheme 23. γ-selective alkylation of α-branched enals.

Seeking to extend the nucleophilic addition at the γ-position of the *in situ* generated dienamine intermediates with other electrophilic species, the same group reported the high stereoselective *γ*-site-selective aldol reaction between *α*-branched enals (**ci** and **ci'**) and isatin **cg** (Scheme 24) *via a* dienamine intermediate using the sterically congested diphenyl prolinol silyl ether **ch** as catalyst.[32] The authors observed that the nature of the *α*-branched enal's substituents led to different product outcome, postulating two plausible divergent mechanisms for the reaction. Using α-alkyl substituted enals **ci**, the 3-substituted 3-hydroxyoxindole derivatives **bi** were obtained with high stereocontrol and selectivity, which could be rationalized through a "steric control" transition state (a pathway, Scheme 24), which is based on the addition of isatin from the unshielded face of intermediate **I** at the *γ*-position. In contrast, *α*-aryl substituted enals (**ci'**) provided access to spirocyclic oxindole scaffols **ck**, with moderate diasteroselectivity, high enantioselectivity (pathway b, Scheme 24) and opposite configuration of the *γ*-stereocenter, which is indicative of a [4+2] cycloaddition transition state (**J**).

[32] C. Cassani, P. Melchiorre, *Org. Lett*, **2012**, *14*, 5590.

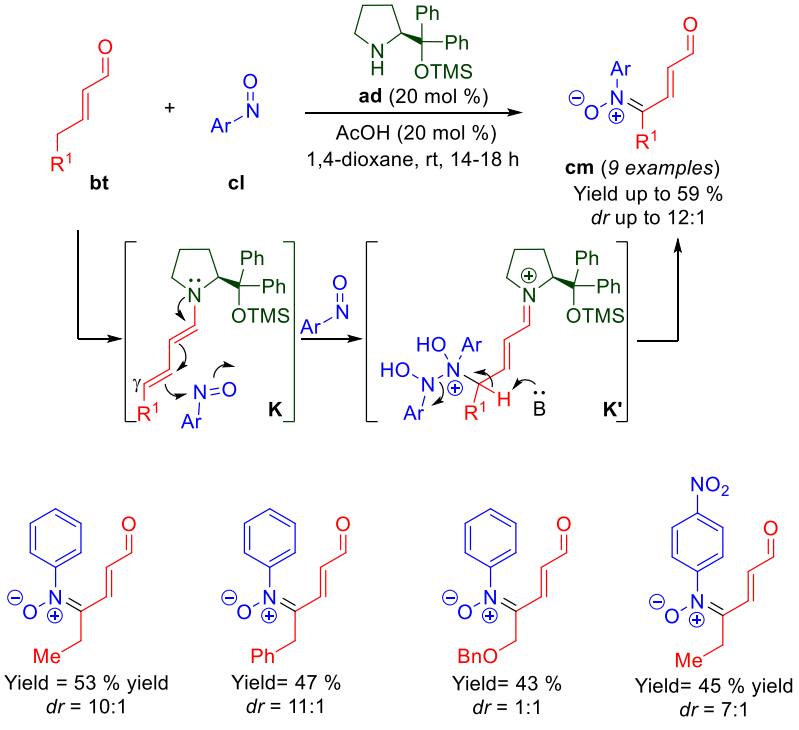


Scheme 24. *γ*-Site-selective aldol reaction between *α*-branched enals and isatin *via* dienamine activation.

Very recently, Brenner-Moyer and colleagues reported the first *γ*-site-selective catalytic reaction to directly introduce nitrone functionality to *α,β*-unsaturated aldehydes *via* dienamine intermediate **K** using catalyst **ad** (Scheme 25).[33] This work represents an unprecedented and useful example of an organocatalytic redox reaction, in which the alkyl and aryl substituted enal (**bk**) is oxidized to the corresponding *γ*-nitrone (**cl**) with moderate yields and diastereoselectivities, thereby reducing the corresponding nitrosoaryl derivative to *N*-arylhydroxylamine. Supported by experimental and theoretical studies, the authors proposed a plausible mechanism, in which the reaction starts with the condensation of the enal **bt** with catalyst **ad**, to form an iminium ion

[33] A. J. Fraboni, S. E. Brenner-Moyer, *Org. Lett*, **2016**,*18*, 2146.

intermediate, which is in equilibrium with the dienamine intermediate (**K**) *via* loss or gain of a proton. Subsequently, the in situ generated dienamine reacts with 2 equivalents of nitrosoaryl compound (**cl**), furnishing intermediate **K'**. However, not evidence to support whether an asynchronous or concerted transition state is involve. Finally, deprotonation of **K'** liberates the nitrone **cm**, along with 1 equivalent of the product of reduction of **bt**.

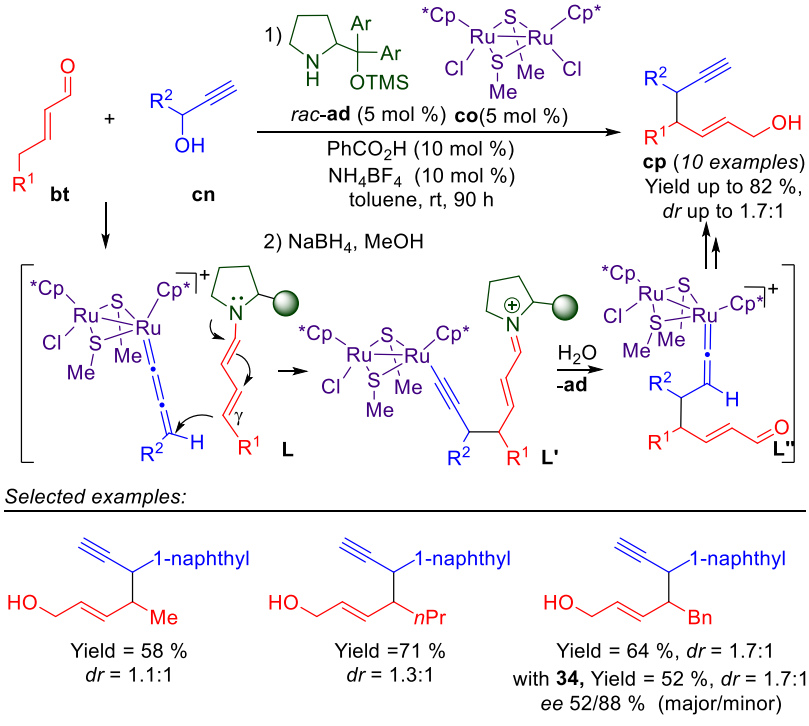


Scheme 25. γ-Site-selective addition of nitrone to α,β-unsaturated aldehydes.

The extension of the asymmetric functionalisation at remote centers of enals by cooperative catalytic processes, involving the combination of dienamine activation with transition-metal catalysis, constitutes an exciting approach to provide a general synthetic technology for designing vinylogous reactions. Pursuing this prospect, the Nishibayashi group developed the γ-site-selective alkylation of γ-enolisable unsaturated aldehydes through cooperative dienamine-metal catalysis (Scheme 26).[34]

[34] M. Ikeda, Y. Miyake, Y. Nishibayashi, *Organometallics*, **2012**, *31*, 3810.

The diruthenium complex **co** in combination with the chiral secondary amine **ad** promoted the γ-selective propargylation of different α,β-unsaturated aldehydes (**bt**) with a broad diversity of propargylic alcohols (**cn**), with good yields, poor diastereoselectivities and moderate enantioselectivities. The author proposed a plausible reaction pathway which start by addition of the dienamine intermediate to the allenylidene complex formed by reaction of the ruthenium complex with the propargyl alcohol (**L**, Scheme 26), leading to an alkynyl vinylidene complex intermediate *via* an alkynyl complex intermediate, which evolve to the γ- alkylated enal by ligand exchange with another propargylic alcohol (**cn**). Compounds (**cp**) were obtained by *in situ* reduction of the aldehydes using $NaBH_4$.

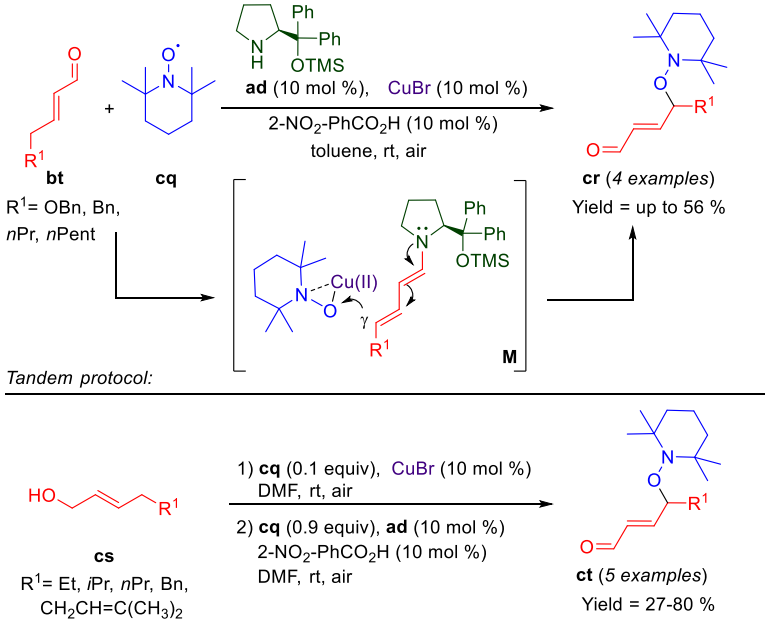


Scheme 26. γ-Propargylation reaction of α,β-unsaturated aldehydes through cooperative ruthenium -dienamine catalysis.

In 2014, a second example of dual dienamine-metal catalysis was reported by Jang and colleague.[35] They developed a multicatalytic reaction where a copper catalyst (CuBr) combined with aminocatalyst **ad** were used to promote both the

[35] X. H. Ho, W. J. Jung, P. K. Shyam, H. Y. Jang, *Catal. Sci. Technol*, **2014**, *4*, 1914.

γ-oxyamination of *α,β*-unsaturated aldehydes (**bt**) (top, Scheme 27). They also developed the one pot aerobic oxidation of allylic alcohols (**bu**/*γ*-oxyamination of *α,β*-unsaturated aldehydes (bottom, Scheme 27) using TEMPO (**bs**) as oxidative reagent. Various allylic alcohols and *α,β*-unsaturated aldehydes were converted to *γ*-oxyaminated *α,β*-unsaturated aldehydes with moderate to good yields. A plausible reaction mechanism for the tandem copper catalysed oxidation and copper-aminocatalysed oxyamination of *α,β*-unsaturated aldehydes was proposed. In the first step, copper–TEMPO complexes are used to oxidize **cq**. The corresponding aldehyde (**bt**) condensates with the aminocatalyst (**ad**), forming the dienamine intermediate. Upon addition of the copper–TEMPO complex to the dienamine intermediate (**M**, Scheme 27), an iminium intermediate is formed, which due to the acidity of the *γ*-carbon isomerised to a dienamine intermediate, preventing further addition of nucleophiles at the *β*-position of the enal. After hydrolysis the desired product **cr** is obtained. Although chiral aminocatalyst (**ad**) was used, stereocontrol was not observed, presumably, due to racemization at the *γ*-position of **cr** during the reaction.

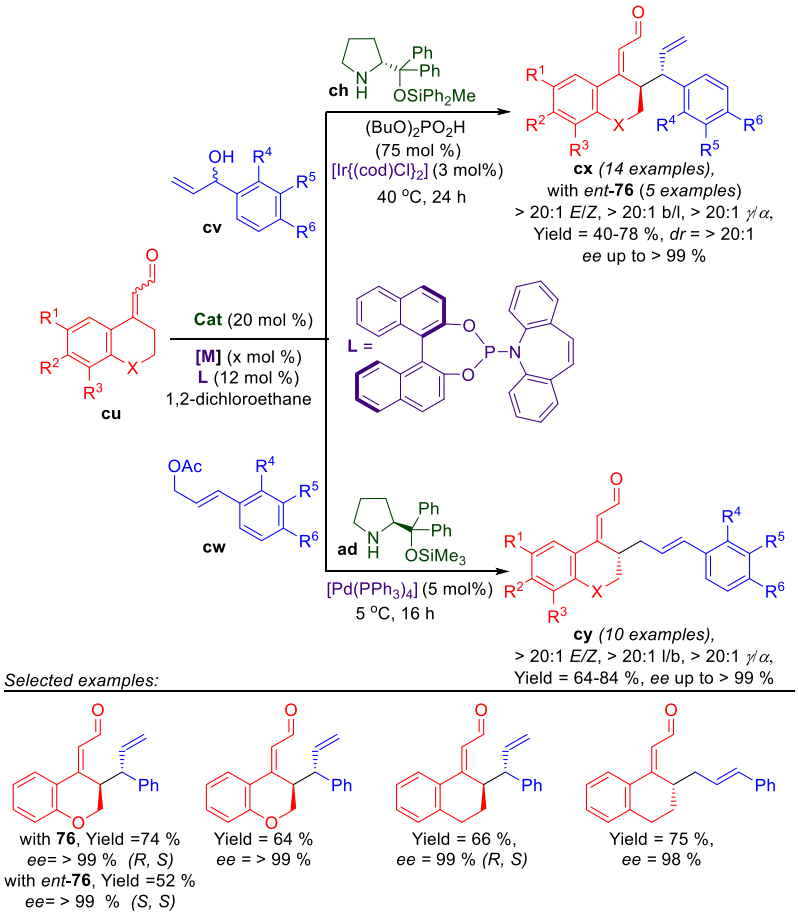


Scheme 27. *γ*-Oxyamination of *α,β*-unsaturated aldehydes and tandem oxidation/*γ*-oxyamination of allylic alcohols via copper-dienamine catalysis.

Recently, Jørgensen's group developed the asymmetric γ-allylation of α,β-unsaturated aldehydes based on combination of dienamine-mediated catalysis and transition-metal catalysis (Scheme 28).[36] This transformation is associated with several potential selectivity issues; the regioselectivity *(α*- versus γ-allylation) of the α,β-unsaturated aldehyde due to the reactive dienamine intermediate contains two nucleophilic sites. Likewise, the activated π-allyl system has two electrophilic sites and the regioselectivity (branched *versus* linear products) of this intermediate also needs to be controlled. Moreover, the control of the *E/Z* ratio, the diastereomeric ratio (for branched products), and enantiomeric excess of the products are a challenge. To overcome the mentioned problems the authors developed a methodology, which provides access to all six isomers of the γ-allylated product (4 stereoisomers of branched products, 2 enantiomers of linear products) in a divergent fashion, in excellent selectivity, by choosing the appropriate combination of aminocatalyst, transition-metal catalyst, and ligand. By the use of aminocatalyst (**ch**) in combination with an iridium catalyst, selective access to branched γ-allylated products (**cx**) was achieved in excellent diastereo- and enantioselectivity.

This approach is based on stereodivergent dual catalysis, and thus allows selective access to both diastereomers of **cx** by using both enantiomers of **ch**. Furthermore, by replacing the iridium catalyst with a palladium catalyst under otherwise similar reaction conditions (aminocatalyst **ad** instead of **ch**) the linear products of the *γ*-allylation (**cy**) were obtained in excellent enantioselectivity.

[36] L. Naesborg, K. S. Halskov, F. Tur, S. M. N. Monsted, K. A. Jørgensen, *Angew. Chem. Int. Ed*, **2015**, *54*, 10193.

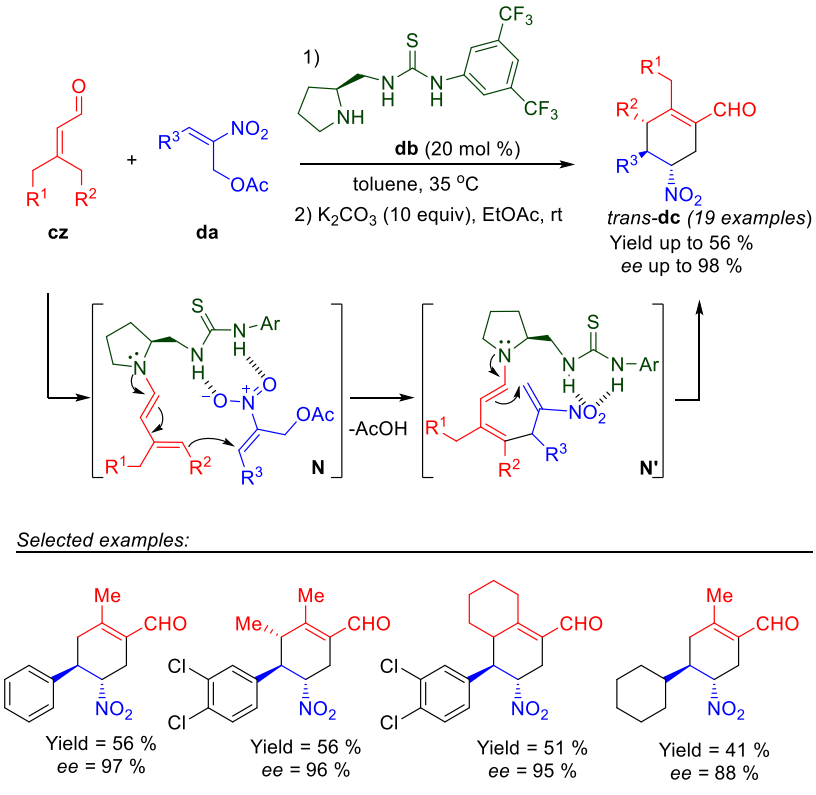


Scheme 28. γ-Allylation of cyclic α,β-unsaturated aldehydes by dual dienamine-transition metal catalysis.

Very recently, Chen's group developed an asymmetric formal α,γ-regioselective [3+3] cycloaddition reaction of α,β-unsaturated aldehydes (**ca**) and 2-nitroallylic acetates (**da**) using chiral bifunctional secondary amine-thiourea **cc** as catalyst. *via* a cascade dienamine-dienamine mediated catalytic reaction (Scheme 29).[37] This cascade reaction proceeds through the generation of the dienamine intermediate (by condensation of **cz** with the aminocatalyst **db**), which reacts with the nitroolefin acceptor (**da**) with complete γ-regioselective. Thus, this first Michael addition step generates the required second acceptor, through the elimination of a molecule of acid, favouring the subsequent a-site selective dienamine-mediated intramolecular catalytic

[37] W. Xiao, X. Yin, Z. Zhou, W. Du, Y. C. Chen, *Org. Lett*, **2016**, *18*, 116.

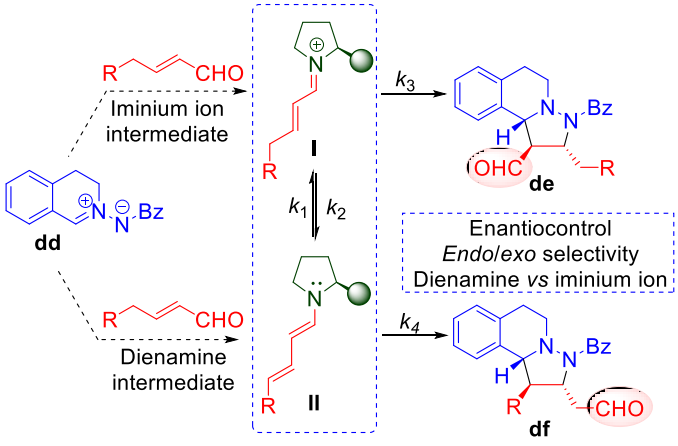
Michael addition to furnish the cyclohexene structures. The formal [3+3] cycloaddition reaction produced cyclohexanes **dc** in moderate yields, excellent enantioselectivities and poor diastereomeric, ratios (*cis/trans*). Both diastereomers were obtained with identical *ee* values, indicating that the enantiocontrol is determined in the first γ-regioselective and the poor diastereocontrol is due to the protonation step. After a simple basic treatment second step, *trans*-**dc** diastereomer was obtained as sole product of the reaction through epimerization of the chiral center adjacent to the NO_2 group of the major diastereomer (*cis*-**dc**).



Scheme 29. Synthesis of *trans*-cyclohexene derivatives *via* a dienamine- dienamine mediated catalytic process.

1.3.2. Precedents of the Group

My group in 2014, developed the [3+2] cycloaddition reaction between azomethine imines and α,β-unsaturated aldehydes through dienamine activation (Scheme 30).[38] Despite the fact that the iminium ion is the previous intermediate for the formation of the corresponding dienamine and that both species are in equilibrium, there were no studies investigating the reactivity control of these two intermediates with their differing nucleophilic and electrophilic natures. In order to have complete control over the plausible equilibrium between the iminium-dienamine (k1 vs. k2) or over the reactivity of both reactions (k3 vs. k4), different reaction conditions were explored (Scheme 30).

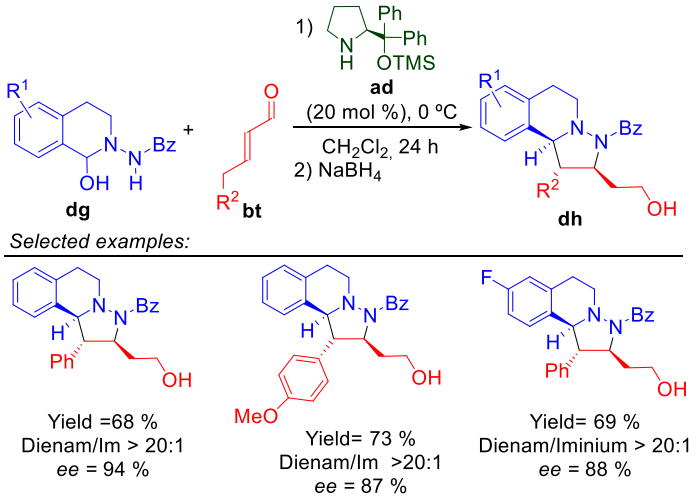


Scheme 30. Dual Reactivity (Iminium-Dienamine) of α,β-unsaturated aldehydes with azomethine imines.

After screening conditions, Alemán's group found that complete control of the dienamine or iminium intermediates could be achieved by employing appropriated conditions. The use of catalyst **ad**, TBAB as an additive and toluene as solvent were the best conditions for iminium type products **de** (top Scheme 30). By contrast, the use of the hydrated dipole **dd**, catalyst **ad** and

[38] C. Izquierdo, F. Esteban, A. Parra, R. Alfaro, J. Alemán, A. Fraile, J. L. García Ruano, *J. Org. Chem.* **2014**, *79*, 10417.

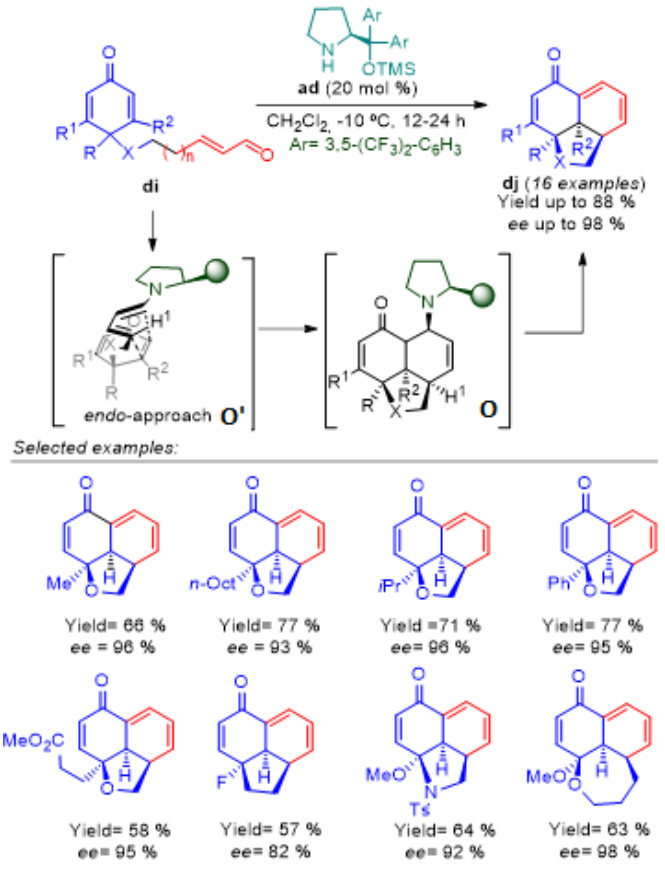
CH_2Cl_2 as solvent are the best conditions so far to obtain dienamine products **df** (Scheme 30). With this work, my group was able to describe the first example of regio-control of an iminium ion intermediate versus a dienamine intermediate in the [3+2] cycloaddition of azomethine imines. Dienamine products (**df**) were achieved with good yield and good enantioselectivity in most cases, regardless of the nature of the aromatic ring used in the aldehydes (**bt**) or the substituent on the aryl group of the azomethine imine (**dg**) (Scheme 31).



Scheme 31.

In the same year, my group also presented the synthesis of tricyclic derivatives (**dj**) (which are presented in different natural and biological products, e.g. momilactone A) by desymmetrisation of cyclohexadienones **di** via dienamine intermediate O' (Scheme 32).[39] The reaction tolerated a large variety of substituents at different positions of the cyclohexadienone **di** and different heterocyclic ring sizes can be achieved. Mechanistic studies by DFT calculations have shown that the reaction proceeds via an asynchronous [4+2] cycloaddition and not a stepwise reaction (intermediate O').

[39] C. Martín-Santos, C. Jarava-Barrera, S. Pozo, A. Parra, S. Díaz- Tendero, R. Más-Ballesté, S. Cabrera, J. Alemán, *Angew. Chem. Int. Ed.* **2014**, *53*, 8184.



Scheme 32. Synthesis of biologically active tricyclic derivatives.

1.4. Background in the synthesis of Diheteroarylalkanes

Despite the great development of organocatalytic methodologies, their application to other areas such medicinal chemistry have rarely been reported although the number of applications has increased in recent years.[40] Because of the absence of transition metals, organocatalytic methods are especially attractive for the preparation of compounds that do not tolerate metal contamination, such us active pharmaceutical compounds.

[40] For reviews in medicinal chemistry see: a) J. Aleman, S. Cabrera, Chem. Soc. Rev. **2013**, *42*, 774. b) R. Marcia de Figueiredo, M. Christmann, *Eur. J. Org. Chem*. **2007**, 2575. c) E. Marques-Lopez, R. P. Herrera, M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138.

In this context, diheteroarylalkanes are natural compounds of tremendous chemical and biological importance, mainly due to their antitumor and analgesics properties, among others (see examples in Figure 4).[41] The structures of these compounds and their potent activity towards a broad number of pharmacological targets make them excellent synthetic targets, especially those containing the substitution 2 and 3´ in both heterocycles (see bottom, Figure 4).[42]

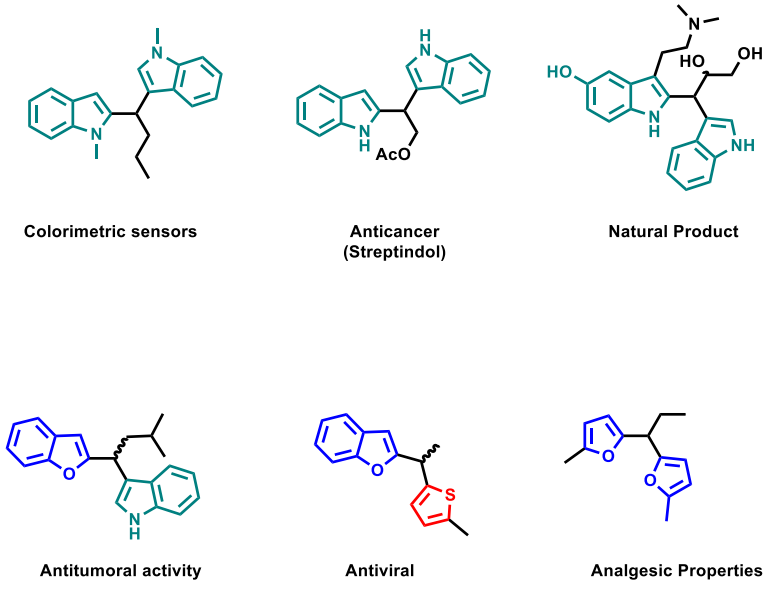
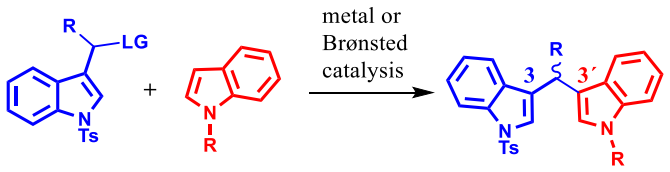


Figure 4. Synthetic significance of Diheteroarylalkanals.

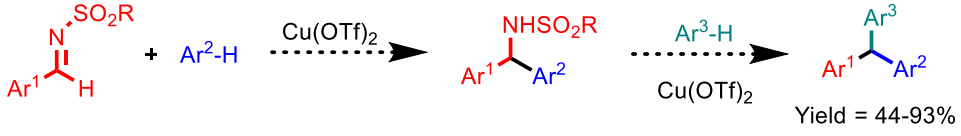
Different approaches have been described for the synthesis of diheteroarylalkanes. The usual approach is based on the Friedel Crafts reaction of indolylmethanol derivatives with an heteroaryl compound in the presence of different metals and also Brønsted acid catalysis (Scheme 33).[43]

[41] S. Dhiman, S. S. V. Ramasastry, *Org. Biomol. Chem*. **2013**, *11*, 8030.
[42] a) S. Dhiman, S. S. V. Ramasastry, Org. Biomol. Chem, **2013**, *11*, 4299. b) G. N. Winston-McPherson, D. Shu, W. Tang, *Bioorg. Med. Chem. Lett*. **2014**, *24*, 4023.
[43] M. H. Zhuo, Y. J. Jiang, Y. S. Fan, Y. Gao, S. Liu, S. Zhang, *Org. Lett*, **2014**, *16*, 1096.



Scheme 33. Approaches for the synthesis of 3 and 3'substituted derivatives.

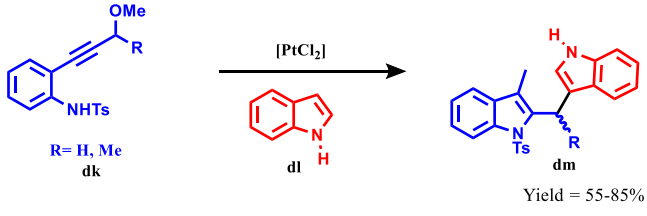
In 2006, Carretero's group developed a novel copper-catalyzed aza-Friedel-Crafts methodology for the synthesis of unsymmetrical diaryl amines and triaryl methanes.[44] The reaction involved *N*-sulfonyl imines as well as two different electron-rich aromatic substrates in a sequential reaction. (Scheme 34).



Scheme 34. Copper-catalyzed Aza-Friedel Craft reaction.

However, this later approach only affords the pattern substitution 3 and 3´ in both heterocycles.

Very recently, in order to achieve the 2 and 3´ substituted compounds, Tang *et al.* started from alkynes,[45] and through a metal catalyzed reaction, the first heterocycle was formed and can be attacked by an indole moiety via a Friedel-Crafts type reaction, forming the desired compounds in a racemic manner (Scheme 35). In any case, these later obtained products were not biological studied.

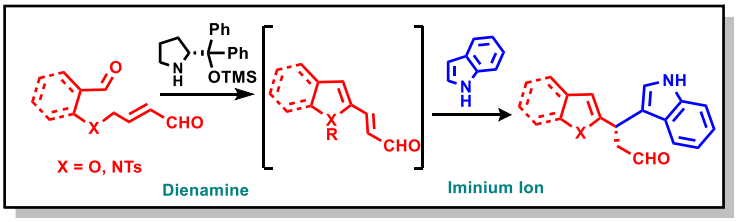


Scheme 35. Metal approaches for the synthesis of 2 and 3' substituted racemic derivatives.

[44] J. Esquivias, R. Gomez Arrayas, J. C. Carretero, *Angew. Chem. Int. Ed*. **2006**, *45*, 629.
[45] H. Li, H. Y. Wang, G. N. Winston-McPherson, H. J. Geng, I. A. Guzei, W. Tang, *Chem. Commun*. **2014**, *50*, 12293.

1.5. Main goal of this chapter

Based on these previous considerations, and in our previous experience in dienamine[46] and iminium ion chemistry,[47] we hypothesized that the use of both reactions for obtaining the 2,3-substituted diheteroaryl compounds would be an appropriate strategy for its synthesis (Scheme 36).



Scheme 36. Main goal of this chapter.

Different reasons make this approach especially attractive:

i) Easy available starting materials (from salicyl aldehydes).

ii) First enantioselective organocatalytic approach,

iii) Modular synthesis of final compounds (X= N, O).

iv) Moreover, we wonder if the final compounds (2, 3´ substitution) would have antitumor activity as it has been shown for other diheteroaryl derivatives (3, 3' substitution). Thus, in this work we present our results in the synthesis of 2, 3´ diheteroaryl compounds using a one pot strategy that include dienamine and iminium ion reaction and also the biological evaluation of the so obtained compounds.

Thus, in this work we present our results in the synthesis of 2, 3´ diheteroaryl compounds using a one pot strategy that include dienamine and iminium ion reaction and also the biological evaluation of the so obtained compounds.

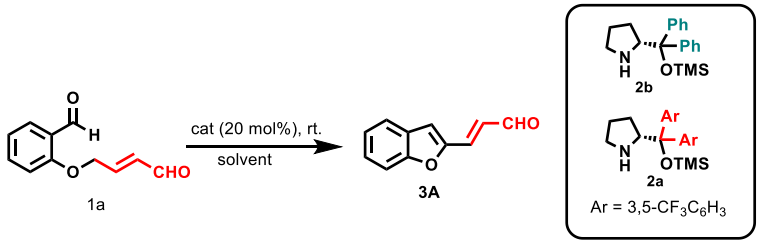
[46] a) C. Jarava-Barrera, S. del Pozo, A. Parra, S. Diaz-Tendero, R. Mas-Balleste, S. Cabrera, J. Alemán, *Angew. Chem. Int. Ed*. **2014**, *53*, 8184. b) C. Izquierdo, A. Parra, R. Alfaro, J. Alemán, A. Fraile, J. L. García Ruano, *J. Org. Chem*. **2014**, *79*, 10417.

[47] J. L. García Ruano, V. Marcos, J.Alemán, *Chem. Commun.*, **2009**, 4435. b) J. L. García Ruano, C. Alvarado, S. Diaz-Tendero, J. Alemán, *Chem. Eur. J.* **2011**, *17*, 4030. c) J. Alemán, C. Alvarado, V. Marcos, A. Nuñez, J. L. García Ruano, *Synthesis*, **2011**, 1840. d) J. Alemán, A. Fraile, L. Marzo, J. L. García Ruano, C. Izquierdo, S. Díaz-Tendero, *Adv. Synth. Catal*. **2012**, *354*, 1665.

1.6. Results and discussion

For our initial experiments, dialdehyde **1A** was employed in the presence of the well-known Jørgensen–Hayashi catalyst **2**;[48] the reactions were stopped at 20 hours (Table 1). Use of the bulkier catalyst **2a** gave **3A** in low yield, but this was increased to 37% through the use of catalyst **2b** (Table 1, entries 1 and 2). The use of other polar solvents such as chloroform, diethyl ether, acetonitrile, or tert-butyl methyl ether did not increase the yield, but employing the more apolar solvent toluene gave the product **3A** in 85% yield with full conversion.

Table 1. Optimization for the dienamine reaction.



Entry	Cat (Ar)	Solvent	Yield [%][b]
1	2a (Ar= 3,5-$(CF_3)_2C_6H_3$)	CH_2Cl_2	20
2	2b (Ar= Ph)	CH_2Cl_2	37
3	2b (Ar= Ph)	$CHCl_3$	53
4	2b (Ar= Ph)	*t*BME	38
5	2b (Ar= Ph)	Et_2O	46
6	2b (Ar= Ph)	CH_3CN	46
7	**2b (Ar= Ph)**	**Toluene**	**85**

[a] All reactions were carried out at 0.02 mmol of **2a** or **2b** and 0.1 mmol of **1a** and 0.1 mL of indicated solvent. [b] Isolated yield after flash chromatography.

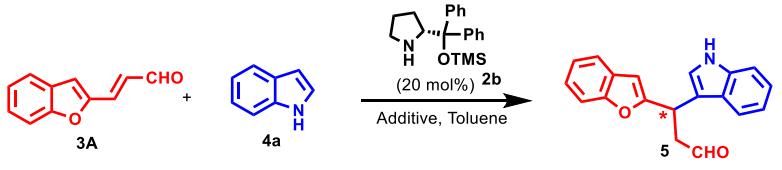
Even though the conversion was complete, the yield was quite low because of the inestability of the product **3A** in column conditions.

Afterwards, we focused our attention in the optimization of the Friedel-Craft reaction, starting from the isolated benzofurane **3A** in the presence of catalyst **2a** (20 mol%).

[48] For a general review, see: K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht, K. A. Jørgensen, Acc. Chem. Res. 2012, 45, 248.

The reaction between **3A** and indole **4a** under the aminocatalyst **2b** led to the desired product **5** in a very low conversion. The nucleophility of the 3 position of the indole **4a** could be increased by the use of an external co-base (Table 2, entries 2-8).[49] Thus, including 100 mol% of Et_3N gave the final product with 52% of conversion and good enantiomeric excess, but a decrease in the amount of this base was beneficial for the conversion (Table 2, entries 2-4). The use of stronger bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave no conversion to the final product, whereas 1,4-diazabicyclo[2.2.2]octane (DABCO) gave the product **4** in moderate conversion (Table 2, entries 6 and 7), which was increased when the amount of this base was decreased up to 20 and 30 mol% (Table 2, entries 8 and 9).

Table 2. Optimization for the Friedel-Craft reaction



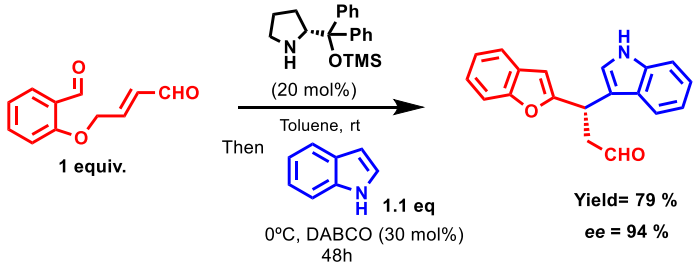
Entry	Base [mol%]	Time [h]	Ee [%][b]	Conv. [%][c]
1	-	36	nd	15
2	Et_3N (100)	72	nd	52
3	Et_3N (50)	72	93	100
4	Et_3N (30)	72	89	100
5	DBU (50)	36	-	-
6	DABCO (75)	36	93	34
7	DABCO (50)	36	95	45
8	**DABCO (30)**	**36**	**94**	**100**
9	DABCO (20)	36	91	100

[a]All reactions were carried out at 0.02 mmol of **2a** or **2b** and 0.1 mmol of **1A** and 0.1 mL of indicated solvent. [b] Determined by SFC. [c] Conversion determined by ^{1}H-NMR.

As I have mentioned above, product **3A** was unstable in column conditions. Therefore, with the one pot reaction, the isolation of intermediate **3A** will be no

[49] We have tried the reaction with the *N*-methylindole without any conversion after 48h. There are examples using co-base for the Friedel-Crafts reaction, see, for example: L. Hong, L. Wang, C. Chen, B. Zhang, R. Wang, *Adv. Synth. Catal*. **2009**, *351*, 772.

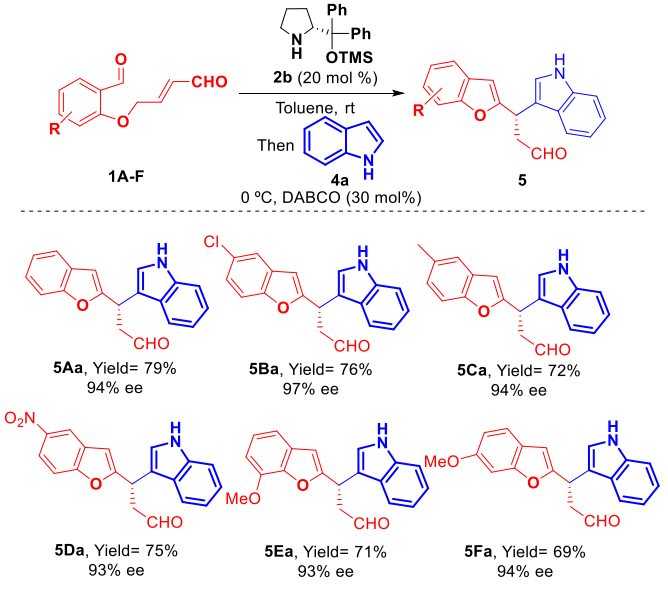
needed. Once we set up the reaction, we were pleased to observe that not only the reaction worked with full conversion, but also with high enantioselectivity (Scheme 37).



Scheme 37.

At this point, with this optimized conditions on hand (Scheme 27) we studied the reaction with a range of aldehydes **1** (Table 3) and indols **4** (Table 4).

Table 3. Different aldehydes 1 in the one-pot reaction.

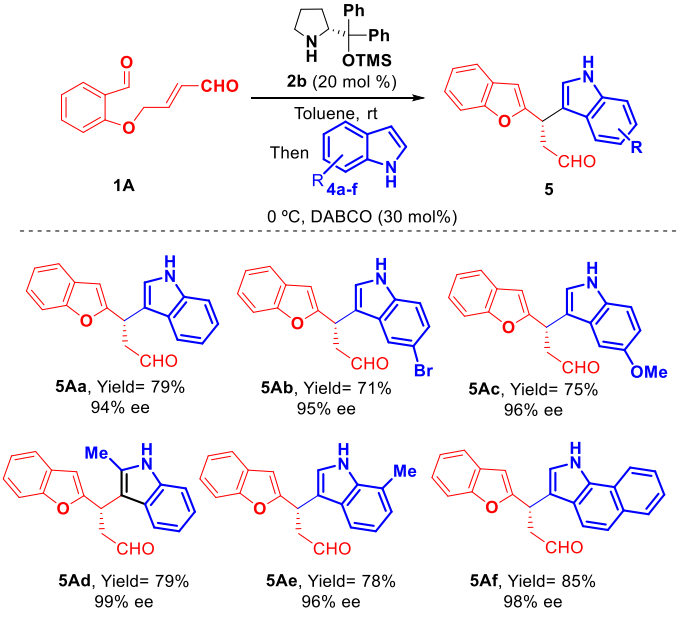


[a] Reaction conditions: **2b** (0.02 mmol), **1** (0.1 mmol), **4** (0.12 mmol), DABCO (0.02 mmol), toluene (0.3 mL). [b] Determined by SFC analysis. [c] Conversion determined by ^{1}H NMR spectroscopic analysis.

The use of starting material with electron-withdrawing groups (EWG) or electron-donating groups (EDG) para to the oxygen atom gave the final products in good yields and enantioselectivities (**5Aa**–**Da**), ranging from 93 to 97%ee.Sub-strates substituted in the ortho and meta position also allowed the synthesis of products **5Ea** and **5Fa** without a decrease in the final *ee* (93–94 %).

We then studied the addition of other indole nucleophiles **4a–f** (Table 4).

Table 4. Different indols 4 in the one-pot reaction.

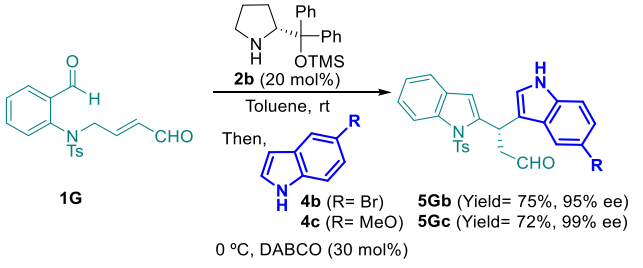


[a]Reaction conditions: **2b** (0.02 mmol), **1** (0.1 mmol), **4** (0.12 mmol), DABCO (0.02 mmol), toluene (0.3 mL). [b] Determined by SFC analysis.[c] Conversion determined by ^{1}H NMR spectroscopic analysis.

Starting indoles with substituents such as bromo (**5Ab**) or methoxy (**5Ac**) groups gave satisfactory yields and *ee* values (> 95% ee). Interestingly, other substituents adjacent to the reactive center (methyl, **5Ad**), and also next to the NH of the indole (which is deprotonated by DABCO in the Friedel–Crafts reaction, **5Ac**) gave products **5Ad** and **5Ae** in excellent enantioselectivities (96 and 99 % *ee*, respectively). The

addition of the 1*H*-benzo[*g*]indole also gave the expected aldehyde **5Af** with excellent *ee*.

The synthesis of bis-indoles was also possible by using this methodology (Scheme 38). Thus, star ting from aldehyde **1G** and using indoles **4b** and **4c** allowed the synthesis of bis-indoles **5Gb** and **5Gc** with excellent enantioselectivity for both cases (95-99% *ee*).



Scheme 38. Synthesis of optically enantioenriched bis-indols by dienamine-Friedel-Crafts one pot reaction.

The absolute configuration of product **5** was determined by X-ray crystallographic analysis of **5Ba**[50] (Figure 5).

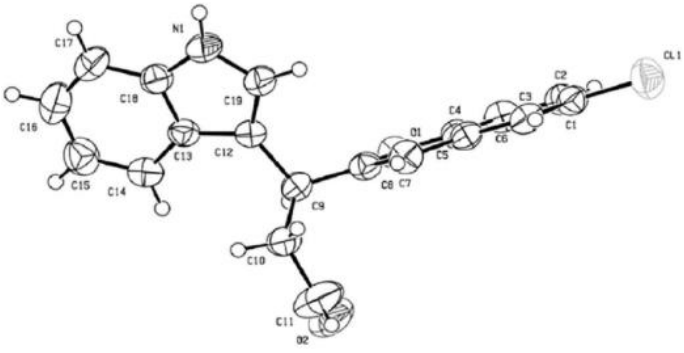
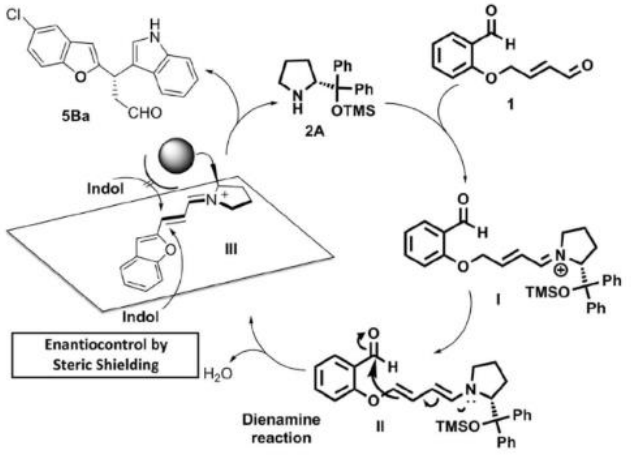


Figure 5. Absolute configuration of product 5Ba.

[50] CCDC-1044397 (**5Ba**).

To explain the stereochemical outcome, we have provided a plausible mechanism in Scheme 39.



Scheme 39. Mechanistic proposal for the synthesis of diheteroarylalkanals.

The reaction starts from aldehyde **1**, which undergoes a condensation reaction with aminocatalyst **2a** to give iminium ion **I**. Isomerization to dienamine **II** can then take place and iminium ion **III** would be generated through intramolecular dienamine condensation and dehydratation. Attack of indole **4** on iminium ion **III** can take placewith enantiocontrol by steric shielding of the bulkier group (CPhPhOTMS) to give the final product **5** (Scheme 39).

1.7. Antitumoral evaluation of diheteroarylalkanals.

From our experience in the synthesis and evaluation of anticancer complexes,[51] and because some similar compounds has revealed biological activity (3,3´-substitution), we decided to carry out the antitumoral-evaluation of this new bisheterocycles compounds with the 2,3´-substitution. The antiproliferative activity of compounds **5** was carried out at La Laguna University (Tenerife) by Dr. José Padrón, and was evaluated against a panel of representative human tumor cell lines including HBL-100

[51] a) J. Aleman, V.Solar, A. Alvarez-Valdes, J. M. Padron, C. Rios-Luci, C. Navarro-Ranninger, MedChemComm, **2011**, *2*, 789. b) C. Martin Santos, S. Cabrera, C. Rios-Luci, J. M. Padron, I. Lopez Solera, A. G. Quiroga, M. A. Medrano

(breast), HeLa (cervix), SW1573 (non-small cell lung) and WiDr (colon), using the SRB assay.[15] The experimental GI_{50} values are outlined in Figures 6 and 7 and compared to those of cisplatin, one of the most important antitumoral compounds in market, after 48 h of treatment (see S.I. for more details). Figure 6 shows the results on antiproliferative activity of compounds with different substitution at the furan aromatic ring (**5Aa-5Fa**) whereas Figure 7 displays the GI_{50} values of compounds with variation in the indole moiety (**5Ab-Af** and **5Gb-5Gc**).

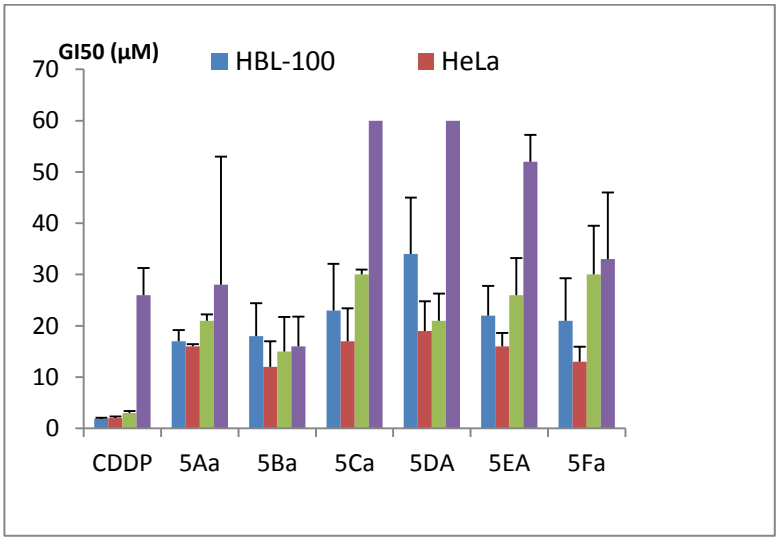


Figure 6. Antiproliferative Activity (GI_{50}, μM) of **5Aa-Fa** in HBL-100 (breast), HeLa (cervix), SW1573 (non-small cell lung) and WiDr (colon) Human Solid Tumor Cells.

The obtained results indicate that the substitution at the aryl moiety of the benzofurane ring has an important effect in the antiproliferative activity of the benzoindol **5**, and this effect depends on the cell line. Thus, the introduction of strong EWGs and EDGs provoked a decrease in the antiprolifertive activity, which was quite remarkable in the case of compounds **5Da** and **5Ea** in WiDr cells. In the case of compounds **5Aa** and **5Ab** the antiproliferative activity was quite high, and was even better than that of Cisplatin for the WiDr cancer cell line,with GI_{50}value of 16 for **5Ba** (**5Ab**–**5Gc**, Figure 6).

Then, we evaluated different substitution at the indole moiety (**5Ab-5Gc**, Figure 7). EDGs provoked a decrease in the antiproliferative activity (**5Ab** and **5Ae**), whereas a methyl group at positions 2 and 7 of the indole moiety increased the biological

activity (**5Ad** and **5Ac**).The bisindol derivatives **5Gb** and **5Gc** gave results that were similar to those of the other benzofurane derivatives **5** (3.5–16 mm). Notably, benzoindole derivative **5Af** was the was the most active in all the cell lines tested (see Figures 7), and was in the same order of magnitude as Cisplatin (2–18 mm); in some cases the GI_{50} was even better than observed with CDDP.This is remarkable in the case of WiDr cell line, which is mutated in p53 and, in general, is more resistant to different anticancer drugs.[52]

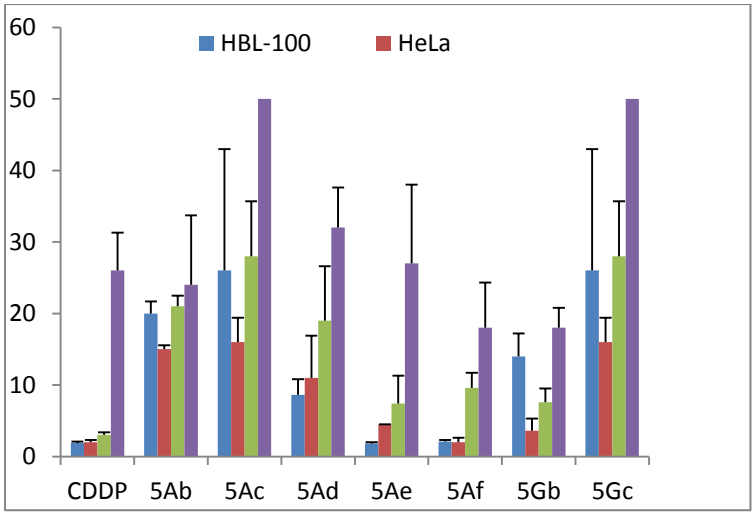


Figure 7. Antiproliferative Activity (GI_{50}, μM) of **5Ab-aF** and **5Gb-Gc** in HBL-100 (breast), HeLa (cervix), SW1573 (non-small cell lung) and WiDr (colon) Human Solid Tumor Cells.

[52] C. Martin Santos, S. Cabrera, C. Rios-Luci, J. M. Padron, I. Lopez Solera, A. G. Quiroga, M. A. Medrano, C. Navarro- Ranninger, J. Aleman, *Dalton Trans*. **2013**, *42*, 13343.

1.8. Conclusions

In summary, we have developed the asymmetric synthesis of diheteroaryl-alkanals through a dienamine-Friedel–Crafts one-pot reaction with good enantioselectivities values and yields. The reaction could tolerate a large variety of substituents at different positions of these new heteroarylalkanals. In addition, we have carried out an antiproliferative analysis of the new compounds, and their structure-activity relationships indicate that these compounds, with the appropriate substitution, are as cytotoxic as Cisplatin. In some cases, such as for the WiDr cancer cell line, which is resistant to CDDP, the antiproliferative activity was superior to that of Cisplatin.

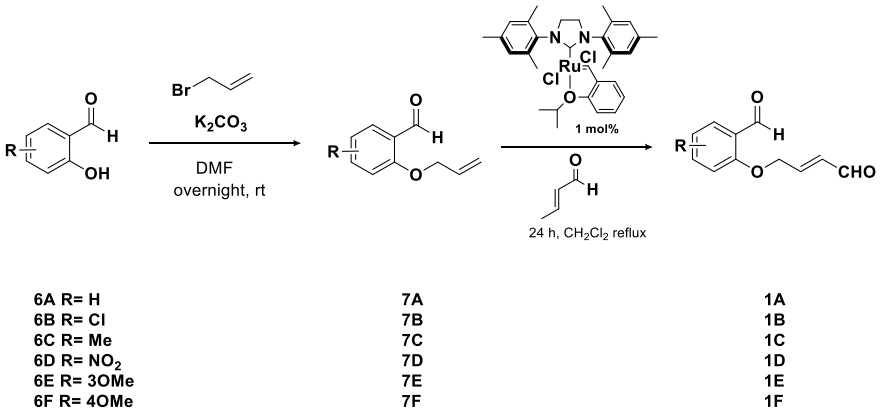
1.9. General Experimental Details

Tetrahydrofuran, toluene, acetonitrile and dichloromethane were purified by passing through a Pure Solv™ column drying system from Innovative Technology, Inc. Additionally, dichloromethane and toluene were dried using activated 4Å molecular sieves and stored under argon. Dry-*tert*-butylmethylether was acquired from commercial sources. 4Å Molecular sieves, 1.6-2.5 mm of particle size, were activated by microwave (700W) (3 x 30 sec) and subsequent cycles of vacuum/argon.

NMR spectra were acquired on a Bruker 300 spectrometer, running at 300, nd 75 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for 1H NMR and 77.2 ppm for ^{13}C NMR respectively). ^{13}C NMR spectra were acquired on a broad band decoupled mode. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septuplet), m (multiplet), br (broad). Mass Spectrometry (MS) was registered in a spectrometer *GCT AgilentTechnologies 6890N* using Electronic Impact (E.I.) and electrospray (ESI+).

For thin layer chromatography (TLC) silica gel plates with fluorescence indicator 254 nm were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in EtOH followed by heating. Flash column chromatography was performed using pore 60 Å, 40-63 μm silica gel and compressed air. Celite® 512 medium was used for some filtration. Hexane and EtOAc were used without previous purification. Optical rotation was recorded in cells with 10 cm path length. The specific solvents and concentrations (in g/100 mL) are indicated. SFC-HPLC analysis was performed with chiral columns (25 cm) using the given conditions.All starting materials were purchased from commercial suppliers without further purification.

1.9.1. Synthesis of Diheteroarylmethanes Starting Materials

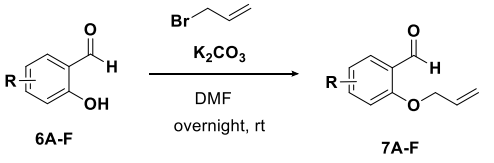


Scheme 40. General procedure for the synthesis of **1A-F.**

1.9.2. General procedure for the synthesis of 2-(allyloxy)-benzaldehyde (7A-F)

The corresponding compound **6** (1 eq.) was dissolved in DMF (25 mL) and to this mixture was added K_2CO_3 (1.5 eq.) and allyl bromide (1.5 eq.). The resulting suspension was stirred at rt overnight. Upon completion (12 h, as determined by TLC, hexanes/dichloromethane 3:1), the reaction mixture was added to a separatory funnel with 40 mL of hexanes and 50 mL of water.

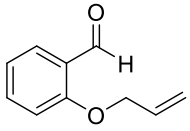
The aqueous phase was extracted (3 x 15 mL hexanes) and the combined organic phases were washed repeatedly with water (5 x 15 mL) and twice with brine (2 x 15 mL). The organic phase was dried (Na_2SO_4) and concentrated to afford the product quantitatively, which was used without further purification.



Scheme 41. Synthesis of **7A-F**.

Spectral Data of substrates 7A-F:

2-(Allyloxy)benzaldehyde (7A)



7A

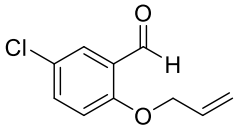
Following the general procedure described above, compound **7A** was obtained in 93% yield as a yellow oil.

^{1}H NMR(300 MHz, $CDCl_3$) δ 10.47 (s, 1H), 7.77 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.46 (t, *J* = 8.5 Hz, 1H), 7.00 (t, *J* = 8.5 Hz, 1H), 6.10-5.90 (m, 1H), 5.42-5.35 (m, 2H), 5.27 (ddd, *J* = 10.6, 2.7, 1.4 Hz, 1H), 4.59 (dt, *J* = 5.1, 1.5 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.7, 161.0, 135.9, 132.4, 128.4, 125.2, 120.9, 118.1, 113.0, 69.2.

EM (TOF-EI$^+$): calculated for $C_{10}H_{10}O_2$: [M^+]:162.0681; found: 162.0677.

2-(Allyloxy)-5-chlorobenzaldehyde (7B)



7B

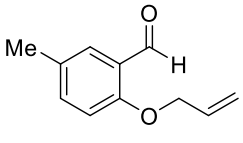
Following the general procedure described above, compound **7B** was obtained in 75% yield as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.44 (s, 1H), 7.76 (d, *J* = 2.6 Hz, 1H), 7.45 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.94-6.85 (m,1H), 5.48-5.20 (m, 2H), 4.65 (dt, *J* = 5.0, 1.5 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$):δ 187.8, 159.2, 135.1, 131.9 127.4, 126.1, 125.7, 118.1, 114.5, 69.4.

EM (TOF-EI$^+$): calculated for $C_{10}H_9ClO_2$: [M^+]:196.0291; found: 196.0295Following the general proceduredescribed above, compound **7A** was obtained in 93% yield as a yellow oil.

2-(Allyloxy)-5-methylbenzaldehyde (7C)



7C

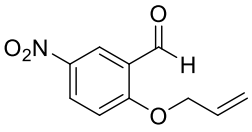
Following the general procedure described above, compound **7C** was obtained in 81% yield as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.5 (s, 1H) , 7.63 (d, *J* = 5.9 Hz, 1H), 7.32 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 5.55-5.40 (m, 2H), 5.38-5.32 (m, 1H), 4.68 (dt, *J* = 3.4, 1.5 Hz, 2H), 2.29 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3, 158.8, 136.3, 132.4, 129.9, 128.0, 124.5, 117.5, 112.7, 68.9, 19.9.

EM (TOF-EI$^+$): calculatedfor $C_{11}H_{12}O_2$: [M^+]:176.0837; found: 176.0835.

2-(Allyloxy)-5-nitrobenzaldehyde (7D)



7D

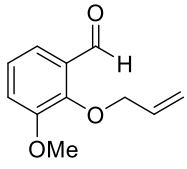
Following the general procedure described above, compound **7D** was obtained in 80% yield as a white oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.59 (d, *J* = 2.9 Hz, 1H), 8.32 (dd, *J* = 9.2, 2.9 Hz, 1H), 7.06 (d, *J* = 9.2 Hz, 1H), 6.05-5.90 (m, 2H), 5.43-5.39 (m, 1H), 4.74 (dt, *J* = 5.2, 1.4 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.6, 164.7, 141.7, 131.1, 130.6, 125.0, 124.8, 119.6, 113.4, 70.4.

EM (TOF-EI$^+$):calculated for $C_{10}H_9NO_4$: [M^+]:207.0532; found: 207.0523.

2-(Allyloxy)-3-methoxybenzaldehyde (7E)



7E

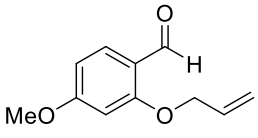
Following the general procedure described above, compound **7E** was obtained in 75% yield as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.47 (s, 1H), 7.56 (d, *J*= 8.6Hz, 1H), 7.19 (t, *J*=6.0 Hz,1H), 7.14 (dd,*J*=8.6,1.9Hz,1H), 6.10-5.90 (m, 1H), 5.60-5.45 (m,2H), 4.69 (d, *J* = 6.0 Hz, 2H), 3.93 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4, 153.0, 151.2, 133.1, 130.2, 124.1, 119.0, 118.8, 118.0, 75.2, 56.0.

EM (TOF-EI$^+$): calculated for $C_{11}H_{12}O_3$: [M^+]:192.078; found: 192.079.

2-(Allyloxy)-4-methoxybenzaldehyde (7F):



7F

Following the general procedure described above, compound **7F** was obtained in 75% yield as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.37 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 6.56 (dd, *J* = 8.7, 1.9 Hz, 1H), 6.45 (d, *J* = 1.8 Hz, 1H), 5.90-5.47 (m, 2H), 5.35-5.20 (m,1H), 4.64 (dt, *J* = 5.0, 1.5 Hz, 2H), 3.87 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.5, 165.7, 162.3, 132.1, 129.8, 118.7, 117.5, 106.0,

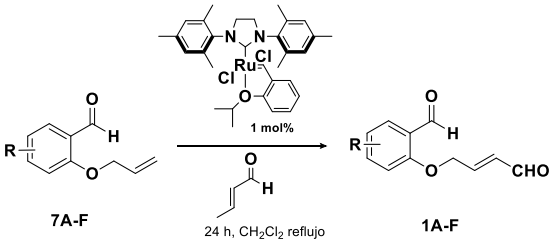
98.5, 68.7, 55.2.

EM (TOF-EI$^+$): calculated for $C_{11}H_{12}O_3$: [M^+]:192.0786; found: 192.0794.

1.9.3. General procedure for the synthesis of (E)-2-((4-Oxobut-2-en-1-yl)oxy)benzaldehyde (1A-F).

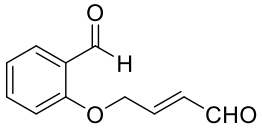
In a sealed tube, the corresponding 2-allyloxybenzaldehyde **7** (1 equiv.) was dissolved in dichloromethane (0.2 M) under argon atmosphere. Then, the crotonaldehyde (6 equiv.) was added dropwise and the solution was degassed. After that, the Hoveyda-Grubbs 2º generation catalyst was added to the solution (0.5 mol%), which was heated to dichloromethane reflux for 24 h.

Then after five hours, a second charge of catalyst was added (0.5 mol%). Upon completion (determined by ^{1}HNMR), the solvent was removed under reducedpressure. The residue was purified by flash column chromatography using Hexane/ AcOEt as eluent.



Scheme 42. Synthesis of **1A-F**.

(*E*)-2-((4-Oxobut-2-en-1-yl)oxy)benzaldehyde (1A)



1A

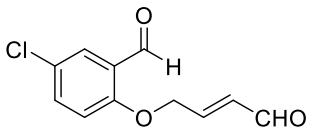
Following the general procedure described above, compound **1A** was obtained in 38% yield as a yellow solid. The crude product was purified by flash column chromatography using 1:1 hexanes / AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.47 (s,1H), 9.69 (d, *J* = 7.6 Hz, 1H), 7.77 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.46 (t, *J* = 8.5 Hz, 1H), 7.00 (t, *J* = 8.5Hz, 1H), 6.01 (dd, *J* = 7.7, 1,8 Hz, 1H), 5.42-5.35 (m,1H), 5.27 (m, 1H), 4.59 (dt, *J* = 5.1, 1.5 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ191.5, 188.0, 158.8, 148.2, 134.9, 131.5, 128.0, 124.2, 120.7, 111.5, 65.8.

EM (TOF-EI$^+$) calculated for $C_{11}H_{10}O_3$: [M^+]:190.0630; found: 190.0638.

(E)-5-Chloro-2-((4-oxobut-2-en-1-yl)oxy)benzaldehyde (1B)



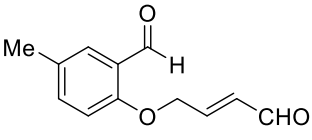
1B

Following the general procedure described above, compound **1B** was obtained in 39% yield as a white solid. The crude product was purified by flash column chromatography using 1:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.44 (s, 1H), 9.69 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 2.6 Hz, 1H), 7.45 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 1H), 5.50-5.40 (m,1H), 5.30-.5.24 (m, 1H), 4.65 (dt, *J* = 5.1, 1.5 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ192.3, 187.6, 158.3, 148.6, 135.4, 132.7, 128.5, 127.4, 126.0, 114.2, 67.2.

EM (TOF-EI$^+$): calculated for $C_{11}H_9O_3Cl$ [M^+]: 224.0240; found: 224.0235.

(E)-5-Methyl-2-((4-oxobut-2-en-1-yl)oxy)benzaldehyde (1C)



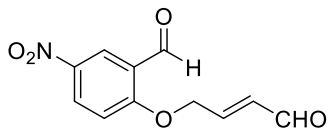
1C

Following the general procedure described above, compound **1C** was obtained in 40% yield as a yellow solid. The crude product was purified by flash column chromatography using 1:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ10.38 (d, *J* = 2.2 Hz, 1H), 9.54 (dd, *J* = 7.7, 2.2 Hz, 1H), 7.52 (s, 1H), 7.25 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.95-6.87 (m,1H), 6.77 (dd,*J* = 7.6, 2.1 Hz, 1H), 6.42-6.32 (m, 1H), 4.83 (dd, *J* = 3.8, 1.9 Hz, 2H), 2.21 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ192.7, 189.2, 158.0, 149.9, 136.6, 132.3, 131.1, 128.9, 124.7, 112.6, 66.9, 20.2.

EM (TOF-EI$^+$): calculated for $C_{12}H_{12}O_3$: [M^+]: 204.0786; found: 204.0777.

(*E*)-5-Nitro-2-((4-oxobut-2-en-1-il)oxi)benzaldehído (1D)



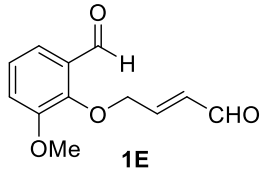
1D

Following the general procedure described above, compound **1D** was obtained in 38% yield as a white solid. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H RMN (300 MHz, $CDCl_3$) δ 10.41 (s, 1H), 9.68 (d, *J* = 7.7 Hz, 1H), 8.59 (d, *J* = 2.9 Hz, 1H), 8.32 (dd, *J* = 9.2, 2.9 Hz, 1H), 7.06 (d, *J* = 9.2 Hz, 1H), 6.05-5.95 (m, 1H), 5.42-5.34 (m,1H), 4.74 (dt, *J* = 5.2, 1.4 Hz, 2H).

^{13}C RMN (75 MHz, $CDCl_3$) δ 192.6, 189.2, 158.0, 149.7, 136.6, 132.4, 131.22, 129.0, 124.8, 112.6, 66.9.

(*E*)-3-Methoxy-2-((4-oxobut-2-en-1-yl)oxy)benzaldehyde (1E)



1E

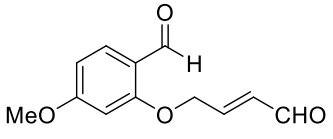
Following the general procedure described above, compound **1E** was obtained in 41% yield as a white solid. The crude product was purified by flash column chromatography using 1:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.39 (s, 1H), 9.62 (d, *J* = 7.8 Hz, 1H), 7.40 (dd, *J*= 5.9, 3.5 Hz, 1H), 7.16 (d, *J* = 2.5 Hz, 1H), 7.04-6.93 (m, 1H), 6.52-6.43 (m,1H), 4.94 (dd, *J* = 4.3, 1.8 Hz, 2H), 3.89 (s, 3H).

^{13}C NMR (75MHz,$CDCl_3$): δ 192.9, 189.5, 152.7, 150.9, 150.3, 132.0, 129.7, 124.7, 119.5, 118.2, 72.2, 56.1.

EM(TOF-EI$^+$):calculated for $C_{12}H_{12}O_4$: [M^+]: 220.073; found: 220.073.

(*E*)-3- (*E*)-4-Methoxy-2-((4-oxobut-2-en-1-yl)oxy)benzaldehyde (1F)



1F

Following the general procedure described above, compound **1F** was obtained in 37% yield as a white solid. The crude product was purified by flash column chromatography using 1:1 hexane/AcOEt as eluent.

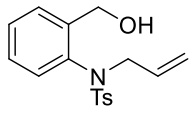
^{1}H NMR (300 MHz, $CDCl_3$) δ 10.37 (s, 1H), 9.58 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 6.56 (dd, *J* = 8.7, 1.9 Hz, 1H), 6.45 (d, *J* = 1.8 Hz, 1H), 5.55-5.45 (m,1H), 5.40-5.30 (m, 1H), 4.64 (dt, *J* = 5.0, 1.5 Hz, 2H), 3.87 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 186.6, 165.0, 160.5, 148.1, 131.5, 130.2, 118.3, 105.4, 98.2, 65.8, 54.7.

EM (TOF-EI$^+$): calculated for $C_{12}H_{12}O_4$: [M^+]:220.0736; found: 220.0726.

***N*-allyl-*N*-(2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (10)**

The *N*-protected 2-aminobenzyl alcohol (1 eq.)[53] was dissolved in DMF (25 mL) and was added K_2CO_3 (1.2 eq.) and allyl bromide(1.05 eq.). The resulting suspension was stirred at rt for 6 h. Upon completion (determined by 3:1 hexanes/dichloromethane), the reaction mixture was added to a separatory funnel with 40 mL of hexanes and 50 mL of water. The aqueous phase was extracted (3 x 15 mL hexane) and the combined organic phases were washed repeatedly with water (5 x 15 mL) and twice with brine (2 x 15 mL). The organic phase was dried ($MgSO_4$) and concentrated to afford **10** quantitatively as a yellow oil that was used without further purification. (Yield=93%).



10

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 3H), 7.26 (m, 4H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.37 (d, *J* = 7.6 Hz, 1H), 5.64 (m, 1H),4.92 (t, *J* = 14.6 Hz, 1H), 4.89-4.85 (m, 2H), 4.44 (d, *J* = 11.7 Hz, 2H), 3.57 (t, *J*= 6.5 Hz, 1H), 2.39 (s, 3H).

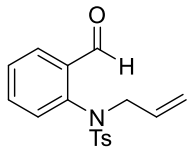
^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 141.4, 136.0, 133.7, 130.9, 130.1, 128.6, 128.0, 127.3, 127.1, 126.6, 118.9, 60.2, 54.1, 20.6.

EM (TOF-EI$^+$): calculated for $C_{17}H_{19}O_3NS$: [M^+]:317.1086; found: 317.1080.

***N*-allyl-*N*-(2-formylphenyl)-4-methylbenzenesulfonamide (11)**

Alcohol **10** was dissolved in CH_2Cl_2 (10 mL) and to this mixture was added MnO_2 (15 eq.) and the resulting suspension was stirred at rt for 5h (TLC conditions: 3:1 (hexane/ AcOEt). After the oxidation was complete, the suspension was filteredthrough a pad of celite on a sintered glass frit of medium porosity. The solvent was removed under reduced pressure to give **11** as a yellow oil (56 % yield).

[53]Alexey Kuznetsov, Anton Makarov, Aleksandr E. Rubtsov, Alexander V. Butin,and Vladimir Gevorgyan, *J. Org. Chem*. **2013**, *78*, 12144.

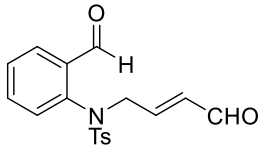


11

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.34 (s, 1H), 7.90 (d, *J* = 6.8 Hz, 1H), 7.37 (dd, *J* = 10.1, 7.5 Hz, 4H), 7.21 (d, *J* = 7.7 Hz, 2H), 6.63 (d, *J* = 7.3 Hz, 1H), 5.95-5.81(m, 1H), 4.96 (dd, *J* = 13.3, 8.1 Hz, 2H), 4.47 (s, 1H), 3.78 (s, 1H), 2.36 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 189.1, 143.3, 140.3, 135.0, 133.3, 133.1, 130.5, 128.7 (2), 127.6, 127.3, 126.8 , 119.4, 53.3, 28.6. **EM (TOF-EI$^+$):** calculated for $C_{17}H_{17}NO_3SNa$: (M^++Na): 338.0824 ; found: 338.0821.

(*E*)-N-(2-formylphenyl)-4-methyl-N-(4-oxobut-2-en-1-yl)benzenesulfonamide (1G)

In a sealed tube, **11** (1eq.) was dissolved in dichloromethane (0.2M) under argon atmosphere. Then, the crotonaldehyde (6 eq.) was added dropwise and the solution was degassed. After that, the Hoveyda-Grubbs 2º generation catalyst (1 mol%) was added to the solution, which was heated to dichloromethane reflux for 24 h. After five hours of reaction, a second charge of catalyst was added. Upon completion (determined by ^{1}H NMR), the solvent was removed under reducedpressure. The residue was purified by flash column chromatography using 1:1 Hexane/AcOEt as eluent. (Yield: 51%).



1G

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.30 (s, 1H), 9.37 (d, *J* = 7.6 Hz, J = 1.4Hz, 1H), 7.91 (dd,*J*= 6.2, 1.4Hz, 1H), 7.42 (d,*J* = 6.2 Hz, 4H), 7.22 (dd,*J* = 6.2, 1.4 Hz, 2H),6.70(dd, *J*=6.2, 1.4 Hz ,1H), 6.64 (dt, *J* = 15.7, 1.4 Hz, 1H), 6.05 (dt,*J*= 15.7, 4.2 Hz, 1H), 4.61 (s, 1H), 4.43 (s, 1H), 2.12 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 188.3, 147.9, 143.8, 139.9, 134.5, 133.80, 133.4, 132.6, 128.9, 128.2, 128.1, 126.9, 126.8, 51.6, 20.6.

EM (TOF-EI$^+$): calculated for $C_{18}H_{17}NO_4SNa$: (M^++Na): 366.0770; found: 366.0770.

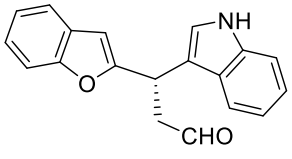
1.9.4. General Procedure for the synthesis of enantioenriched diheteroarylmethanes 5.

The corresponding (*E*)-4-oxobut-2-en-1-yl)oxy)benzaldehyde **1A-G** (1.0 eq.) and (*R*)-α-α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **2b** (20 mol%) were dissolved in 0.3 ml of toluene. The resulting mixture was stirred at room temperature overnight. Then, indole **4a-f** (1.1 eq.), DABCO (30 mol %) and 0.2 ml of toluene were added to the solution at 0ºC. Upon completion (72 h determined by TLC), the solvent was removed under reduced pressure. The residue was purified by flash column chromatography using 3:1 Hexane/ AcOEt as eluent.

In all cases the enantiomeric excesses were determined in the corresponding alcohols, following this procedure: a solution of the corresponding aldehyde in methanol (0.5 ml) was added sodium borohydride (5 equiv.).

Upon completion (45 min, as determined by TLC, Hexanes/AcOEt 3:1), the reaction mixture was added to a separatory funnel with 5 mL of dichloromethane and 5 mL of water. The aqueous phase was extracted (5 x 5 mL Dichloromethane) and the combined organic phases were washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated to afford the product quantitatively, which was used without further purification.

(*S*)-3-(Benzofuran-2-yl)-3-(1*H*-indol-2-yl)propanal (5Aa)



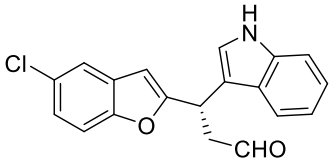
5Aa

Following the general procedure described above, compound **5Aa** was obtained in 79% yield as a red oil. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, J = 1.8 Hz, 1H), 8.06 (bs, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.40-7.32 (m, 3H), 7.12-7.09 (m, 5H), 6.33 (s, 1H), 4.98 (t, J = 7.3 Hz, 1H), 3.32 (dd,J = 10.4, 6.1 Hz, 1H), 3.21 (dd, J = 10.8, 6.3 Hz, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.8, 158.1, 153.7, 135.4, 127.5, 125.0, 122.64, 121.6, 121.4, 121.3, 119.6, 118.7, 118.1, 113.8, 110.4, 109.9, 102.1, 46.2, 30.3. **EM (TOF-EI+):** calculated for $C_{19}H_{15}NO_2$: $[M^+]$:289.1103; found:

289.1115. $[\alpha]_D^{20}$= + 40.73 (c = 0.71, $CHCl_3$).The enantiomeric excess was determined by SFC previous reduction of the obtained aldehyde using Chiralpak-IB-3-15-20 column [CO_2/MeOH (85:15), 3.0 mL/min]: τ_{minor}= 13.81min, τ_{major}= 15.35 min. (94% *ee*).

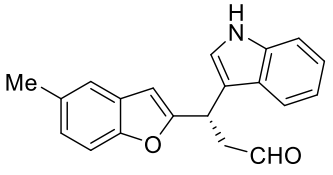
(*S*)-3-(5-Chlorobenzofuran-2-yl)-3-(1*H*-indol-3- yl)propanal (5Ba)



5Ba

Following the general procedure described above, compound **5Ba** was obtained in 76% yield as a red oil. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.05 (bs, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.30-7.24 (m, 3H), 7.10-7.05 (m, 4H), 6.25 (s, 1H), 4.96 (t, J = 7.1 Hz, 1H), 3.24 (dd, J= 10.3, 6.4 Hz, 1H) 3.12 (dd, J =10.4, 6.1 Hz, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.5, 160.8, 153.2, 136.5, 129.9, 128.2, 126.0, 123.8, 122.6, 122.4, 120.3, 119.9, 119.1, 114.5, 111.9, 111.5, 102.8, 47.2, 31.32. **EM (TOF-EI+):** calculated for $C_{19}H_{14}ClNO_2$: [M+]:323.0713; found: 323.0707. $[\alpha]_D^{20}$= +62.3 (c = 1.56, $CHCl_3$). The enantiomeric excess was determined by SFC previous reduction of the obtained aldehydeusing Chiralpak-IB-3-15-20 column [CO_2/MeOH (85:15), 3.0 mL/min]: τ_{minor}= 15.72 min, τ_{major}= 16.27min. (97% *ee*).

(*S*)-3-(1H-Indol-3-yl)-3-(5-methylbenzofuran-2-yl)propanal (5Ca)

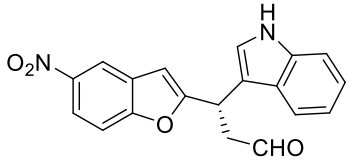


5Ca

Following the general procedure described above, compound **5Ca** was obtained in 72% yield as a red oil. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.01 (bs, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J*= 8.1 Hz, 1H), 7.20-7.15 (m, 3H), 7.02-6.99 (m, 3H), 6.25 (s, 1H), 4.97 (t, *J* = 7.3 Hz, 1H), 3.32 (dd, *J* = 9.5, 7.1, 1H) 3.20 (dd, *J* = 9.7, 7.3, 1H), 2.28 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.9, 159.1, 153.2, 136.5, 132.1, 128.6, 126.1, 124.8, 122.5, 122.3, 120.5, 119.8, 119.2, 114.9, 111.4, 110.5, 102.9, 47.3, 31.4, 26.9**. EM (TOF-EI+):** calculated for $C_{20}H_{17}NO_2$: [M^+]: 303.1259;

found: 303.1261. $[\alpha]_D^{20}$= +64.25 (c = 0.69, $CHCl_3$).The enantiomeric excess was determined by SFC previous reduction of the obtained aldehyde using Chiralpak-IB-3-15-20 column [CO_2/MeOH (85:15), 3.0 mL/min]: τ_{minor}= 14.47 min, τ_{major}= 15.43 min. (94% *ee*).

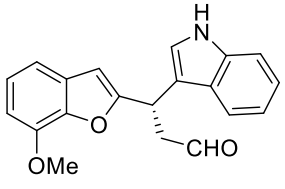
(*S*)-3-(1H-Indol-3-yl)-3-(5-nitrobenzofuran-2-yl)propanal (5Da)



5Da

Following the general procedure described above, compound **5Da** was obtained in 75% yield as a red oil. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.52 (bs, 1H), 8.31 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.63 (d, J = 9.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.40-7.37(m, 3H), 7.28 (t, *J* = 7.5 Hz, 1H), 5.28 (t, *J* = 7.2 Hz, 1H), 3.52 (dd, J = 9.3, 6.9 Hz, 1H), 3.48 (dd, *J* = 9.5, 7.1 Hz, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.8, 161.9, 156.6, 143.1, 135.5, 127.9, 124.8, 121.7, 121.4, 118.9, 118.7, 117.9, 116.1, 112.9, 110.6, 110.3, 102.8, 45.9,30.2. **EM (TOF-EI+):** calculated for $C_{19}H_{14}N_2O_4$: [M^+] 334.0954; found: 334.0963. $[\alpha]_D^{20}$= +50.0 (c = 0.58, $CHCl_3$).The enantiomeric excess was determined by SFC previous reduction of the obtained aldehyde using Chiralpak-IB-3-15-40 column [CO_2/MeOH (85:15), 3.0 mL/min]: τ_{minor}= 21.94 min,τ_{major}= 22.97 min. (93% *ee*).

(*S*)-3-(1H-Indol-3-yl)-3-(7-methoxybenzofuran-2-yl)propanal (5Ea)

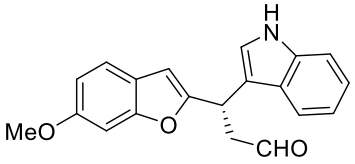


5Ea

Following the general procedure described above, compound **5Ea** was obtained in 71% yield as a red oil. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.38 (bs, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.50 (s, 1H), 7.43 (dd, *J* = 13.7, 6.4 Hz, 1H), 7.33 (m, 4H), 6.99 (d, *J* = 7.7 Hz, 1H), 6.61 (s, 1H), 5.34 (t, *J* = 7.3 Hz, 1H), 4.20 (s, 3H), 3.52 (dd, *J* = 9.5, 7.1 Hz, 1H), 3.48 (dd, *J* = 9.5, 7.1Hz, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.8, 158.2, 144.0, 142.9, 135.4, 129.2, 125.0, 122.3, 121.5, 121.4, 118.7, 118.2, 113.6, 112.1, 110.3, 105.0, 102.7, 54.9, 46.3, 30.3. **HRMS**

(ESI+): calculated for $C_{20}H_{17}NO_3Na$ (M^++Na): 342.1110; found: 342.1100. $[\alpha]_D^{20}$= + 25.3 (c = 0.61, $CHCl_3$). The enantiomeric excess was determined by SFC previous reduction of the obtained aldehyde using Chiralpak-IB-3-15-20 column [CO_2/MeOH (85:15), 3.0 mL/min]: τ_{minor}= 17.27 min, τ_{major}= 18.36min. (93% *ee*).

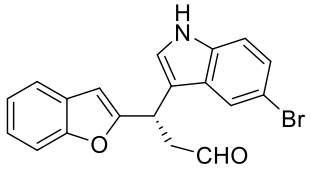
(*S*)-3-(1*H*-Indol-3-yl)-3-(6-methoxybenzofuran-2-yl)propanal (5Fa)



5Fa

Following the general procedure described above, compound **5Fa** was obtained in 69% yield as a red oil. The crude product was purified by flash column chromatography using 3:1 hexanes / AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.03 (bs, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.04 (dd, *J* = 14.1, 4.8 Hz, 2H), 6.90 (s, 1H), 6.74 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.29 (s, 1H), 4.97 (t, *J* = 7.3 Hz, 1H), 3.78 (s, 3H), 3.26 (dd, *J* = 9.3, 6.9 Hz, 1H), 3.14 (dd, *J* = 9.5, 7.1 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.9, 157.0, 156.5, 154.7, 135.4, 125.1, 121.4, 121.2, 120.7, 119.6, 118.7, 118.2, 114.0, 110.4, 110.3, 101.8, 94.9, 54.7, 46.3, 30.3. **HRMS (ESI+):** calculated for $C_{20}H_{17}NO_3Na$ (M^++Na): 342.1105; found: 342.1100. $[\alpha]_D^{20}$= + 32.50 (c = 0.74, $CHCl_3$).The enantiomeric excess was determined by SFC previous reduction of the obtained aldehyde using Chiralpak-IB-2-10-80 column [CO_2/MeOH (90:10), 2.0 mL/min]: τ_{minor}= 55.98 min, τ_{major}= 58.60 min. (94% *ee*).

(*S*)-3-(Benzofuran-2-yl)-3-(5-bromo-1*H*-indol-3-yl)propanal (5Ab)

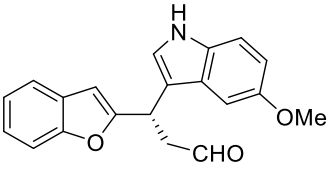


5Ab

Following the general procedure described above, compound **5Ab** was obtained in 71% yield as a red oil. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.65 (t, J = 1.7 Hz, 1H), 8.07 (bs, 1H), 7.55 (d, *J* = 23.7 Hz, 1H), 7.30-7.28 (m, 2H), 7.10-7.05 (m, 5H), 6.24 (s, 1H), 4.85 (t, *J* = 7.3 Hz, 1H), 3.21 (dd, *J* = 9.4, 7.1 Hz, 1H), 3.09 (dd, *J* = 9.7, 7.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.4 158.6, 154.8 135.1, 128.4, 127.8, 125.4, 123.8, 123.6, 122.7, 121.7, 120.7, 114.6, 113.1, 112.9, 111.0, 103.2, 47.2, 31.1. **EM**

(TOF-EI+): calculated for $C_{19}H_{14}BrNO_2$: [M+]: 367.0208; found: 367.0203. $[\alpha]_D^{20}$= + 49.9 (c = 1.28, CHCl3).The enantiomeric excess was determined by SFC previous reduction of the obtained aldehyde using Chiralpak-IA-3-20-20 column [CO_2/MeOH (80:20), 3.0 mL/min]: τ_{minor}= 8.37min,τ_{major}=6.91min.(95% *ee*).

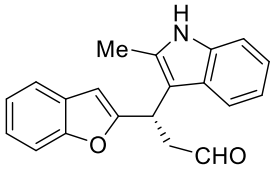
(*S*)-3-(Benzofuran-2-yl)-3-(5-methoxy-1*H*-indol-3-yl)propanal (5Ac)



5Ac

Following the general procedure described above, compound **5Ac** was obtained in 75% yield as a red oil. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEtas eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.94 (bs, 1H), 7.40- 7.35 (m, 2H), 7.18-7.13 (m, 3H), 6.98 (d, *J* = 7.6 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.33 (s, 1H), 4.95 (t, *J* = 7.2 Hz, 1H), 3.74 (s, 3H), 3.25 (dd, *J* = 9.6, 7.0 Hz, 1H), 3.19 (dd, *J* = 9.6, 7.0 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.8, 158.0, 153.8, 153.1, 130.5, 127.5, 125.52, 122.6, 122.0, 121.6, 119.6, 113.5, 111.5, 111.0, 109.9, 102.1, 100.1, 54.8, 46.2, 30.3. **EM (TOF-EI+):** calculated for $C_{20}H_{17}NO_3$: [M^+] 319.1208; found: 319.1221. $[\alpha]_D^{20}$= +46.6 (c = 0.71, $CHCl_3$). The enantiomeric excess was determined by SFC previous reduction of the obtained aldehyde using Chiralpak-IA-3-20-20 column [CO_2/MeOH (80:20), 3.0 mL/min]: τ_{minor}= 8.28 min, τ_{major}= 6.44 min. (96% *ee*).

(*S*)-3-(Benzofuran-2-yl)-3-(2-methyl-1*H*-indol-3-yl)propanal (5Ad)

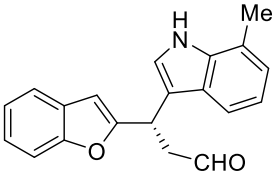


5Ad

Following the general procedure described above, compound **5Ad** was obtained in 78% yield as a red oil. The crude product was purified by flash column chromatography using 3:1 hexane/ AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.82 (bs, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.37-7.34 (m, 1H), 7.21-7.19 (m, 1H), 7.14-7.06(m, 5H), 6.31 (s, 1H), 4.97 (t, *J* = 11.1 Hz,1H), 3.35 (*J* = 9.4, 6.9 Hz, 1H), 3.25 (dd, *J* = 9.6, 7.0 Hz, 1H), 2.38 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.6, 158.2, 153.7, 134.4, 131.3, 127.6, 125.9, 122.5, 121.5, 120.1, 119.5, 118.4, 117.8, 109.9, 109.5, 108.6, 102.1, 45.7, 29.6, 11.0. **HRMS (ESI+):** calculated for $C_{20}H_{17}NO_2Na$ (M^++Na): 326.1157; found: 326.1151.

$[\alpha]_D^{20}$= +26.9 (c = 0.72, $CHCl_3$). The enantiomeric excess was determined by SFC previous reduction of the obtained aldehyde using Chiralpak-IB-3-15-20 column [CO_2/MeOH (85:15), 3.0 mL/min]: τ_{minor}= 13.10 min, τ_{major}= 14.32min. (96% *ee*).

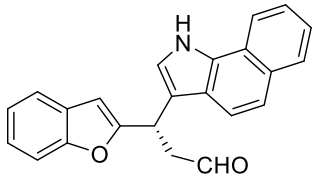
(*S*)-3-(Benzofuran-2-yl)-3-(7-methyl-1*H*-indol-3- yl)propanal (5Ae)



5Ae

Following the general procedure described above, compound **5Ae** was obtained in 79% yield as a red oil. The crude product was purified by flash column chromatography using 3:1 hexane/ AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.98 (bs, 1H), 7.40-7.35 (m, 3H), 7.16-7.12 (m, 4H), 6.95 (dd, *J* = 8.3, 5.0 Hz, 1H), 6.34 (s, 1H), 4.99 (t, *J* = 7.3 Hz, 1H), 3.40 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.22 (dd, *J* = 9.9, 7.3 Hz, 1H), 2.41 (d, *J* = 1.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.8, 159.1, 154.8, 136.1, 128.5, 125.6, 123.6, 123.0, 122.6, 122.0, 120.6, 120.6, 120.0, 116.9, 115.4, 111.0, 103.1, 47.3, 31.5, 16.5. **EM (TOF-EI+):** calculated for $C_{20}H_{17}NO_2$: [M^+] 303.1259; found: 303.1247. $[\alpha]_D^{20}$= +38.8 (c = 0.56, $CHCl_3$).The enantiomeric excess was determined by SFC previous reduction of the obtained aldehyde using Chiralpak-IB-3-15-40 column [CO_2/MeOH (85:15), 3.0 mL/min]:τ_{minor} =11.44 min, τ_{major}= 12.52 min. (99% *ee*).

(*S*)-3-(1*H*-Benzo[*g*]indol-3-yl)-3-(benzofuran-2-yl)propanal (5Af)

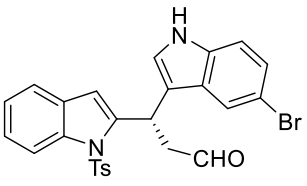


5Af

Following the general procedure described above, compound **5Af** was obtained in 85% yield as a red oil. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.85 (bs, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.80 (dd, *J* = 9.9, 4.7 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.46-7.41 (m, 2H), 7.36-7.33 (m, 2H), 7.16-7.12 (m, 4H), 6.42 (s, 1H), 5.06 (t, *J* = 11.2 Hz, 1H), 3.40 (dd, *J* = 9.5, 7.0 Hz, 1H) 3.23 (dd, *J* = 9.2, 7.0 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.8, 158.2, 153.8, 130.2, 129.5, 127.8, 127.5, 124.6, 123.2, 122.7, 121.6, 121.0, 120.7, 119.7, 119.6, 119.4, 118.4, 117.9, 115.6, 110.0, 102.2, 46.5, 30.4. **HRMS (ESI+):** calculated for $C_{23}H_{17}NO_2Na$ (M^++Na): 362.1162; found: 362.1151.

$[\alpha]_D^{20}$= +16.0 (c = 0.69, $CHCl_3$). The enantiomeric excess was determined by SFC previous reduction of the obtained aldehyde usingChiralpak-IB-3-15-40 column [CO_2/MeOH (85:15), 3.0 mL/min]: τ_{minor}= 25.38min,τ_{major}= 27.02min. (98% *ee*).

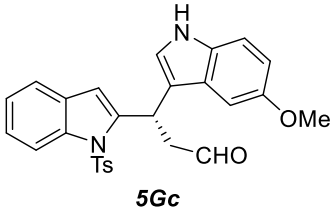
(*S*)-3-(5-Bromo-1*H*-indol-3-yl)-3-(1-tosyl-1*H*-indol-2-yl)propanal (5Gb)



5Gb

Following the general procedure described above, compound **5Gb** was obtained in 75% yield as a red oil. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.70 (d, *J* = 3.0 Hz, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.07 (bs, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.29-7.25 (m, 2H), 7.20-7.15 (m, 5H), 6.94 (d, *J* = 1.8 Hz, 1H), 6.82 (s, 1H), 6.06 (s, 1H), 5.38 (dd, *J* = 9.5, 4.2 Hz, 1H), 3.44 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.02 (dd, *J* = 9.6, 3.1 Hz, 1H), 2.30 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.7, 144.4, 141.6, 137.1, 134.9, 134.1, 129.2 (2), 128.2, 126.9, 125.1 (2), 124.4, 123.7, 122.9, 122.8, 120.5, 119.6, 114.6, 114.3, 111.9, 111.7, 110.4, 48.5, 29.7, 20.8. **HRMS (ESI+):** calculated for $C_{26}H_{21}BrN_2O3SNa$ (M^++Na):543.0343; found: 543.0348. $[\alpha]_D^{20}$= + 90.8 (c = 1.62, $CHCl_3$). The enantiomeric excess was determined by SFC previous reduction of the obtained aldehyde using Chiralpak-IC-3-15-30 column [CO_2/MeOH (85:15), 3.0 mL/min]: τ_{minor}= 13.3min, τ_{major}= 15.02min. (95% *ee*).

(*S*)-3-(5-Methoxy-1*H*-indol-3-yl)-3-(1-tosyl-1*H*-indol-2-yl)propanal (5Gc)



5Gc

Following the general procedure described above, compound **5Gc** was obtained in 72% yield as a red oil. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.68(s, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 7.93 (bs, 1H), 7.50 (d, *J* = 6.8 Hz, 1H), 7.24-7.20 (m, 5H), 7.03 (d, *J* = 7.3 Hz, 2H), 6.83 (s, 1H), 6.74 (d, *J* = 8.8 Hz, 1H), 6.44 (s, 1H), 6.23 (s, 1H), 5.48 (d, *J* = 5.9 Hz, 1H), 3.58 (s, 3H), 3.32 (dd, *J* = 9.8, 7.0 Hz, 1H), 3.04 (dd, *J* = 9.8, 6.1 Hz, 1H), 2.23 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.1, 152.9, 143.8, 142.1, 136.8, 135.1, 130.7, 128.7 (2), 128.3, 125.6, 125.3 (2), 123.5, 122.7, 122.7, 119.5, 114.6,

114.1, 110.9, 110.8, 109.9, 100.8, 54.8, 48.6, 29.7, 20.5. **HRMS (ESI+):** calculated for $C_{27}H_{24}N_2O_4SNa(M^+ + Na)$: 495.1347; found:495.1349. $[\alpha]_D^{20}$= +57.9 (c = 0.74, $CHCl_3$).The enantiomeric excess was determined by SFC previous reduction of the obtained aldehyde using Chiralpak-IA-3-15-30 column [CO_2/MeOH (85:15), 2.0 mL/min]: τ_{minor}= 18.5 min, τ_{major}= 19.68 min. (99% *ee*).

1.10. Biological studies

All starting materials were commercially available research grade chemicals and used without further purification. RPMI 1640 medium was purchased from Flow Laboratories (Irvine, UK), fetal calf serum (FCS) was from Gibco (Grand Island, NY), trichloroacetic acid (TCA) and glutamine were from Merck (Darmstadt, Germany), and penicillin G, streptomycin, DMSO and sulforhodamine B (SRB) were from Sigma (St Louis, MO).

1.10.1. Cells, culture and plating

The human solid tumor cell lines HBL-100, HeLa, SW1573 and WiDr were used in this study. These cell lines were a kind gift from Prof. G. J. Peters (VU Medical Center, Amsterdam, The Netherlands). Cells were maintained in 25 cm2 culture flasks in RPMI 1640 supplemented with 5% heat inactivated fetal calf serum and 2 mM L-glutamine in a 37 ºC, 5% CO_2, 95% humidified air incubator. Exponentially growing cells were trypsinized and re-suspended in antibiotic containing medium (100 units penicillin G and 0.1 mg of streptomycin per mL). Single cell suspensions displaying >97% viability by trypan blue dye exclusion were subsequently counted. After counting, dilutions were made to give the appropriate cell densities for inoculation onto 96-well microtiter plates. Cells were inoculated in a volume of 100 µL per well at densities of 10 000 (HBL-100, HeLa and SW1573) and 20 000 (WiDr) cells per well, based on their doubling times.

1.10.2. Chemosensitivity testing

Compounds were initially dissolved in DMSO at 400 times the desired final maximum test concentration. Control cells were exposed to an equivalent

concentration of DMSO (0.25% v/v, negative control). Each agent was tested in triplicate at different dilutions in the range of 1–100 μM. The drug treatment started on day 1 after plating. Drug incubation times were 48 h, after which cells were precipitated with 25 μL ice-cold TCA (50% w/v) and fixed for 60 min at 4ºC. Then the SRB assay was performed. The optical density (OD) of each well was measured at 492 nm, using BioTek'sPowerWave XS Absorbance Microplate Reader. Values were corrected for background OD from wells only containing medium.

Table 5. Antiproliferative Activity (GI_{50}, μM) of compounds **5** in Comparison to CDDP in Human Solid Tumor Cells.

Compound	HBL-100	HeLa	SW1573	WiDr
CDDP	1.9 (± 0.16)	2.0 (± 0.32)	3.0 (± 0.37)	26 (± 5.3)
5Aa	17 (± 2.2)	16 (± 0.4)	21 (± 1.2)	28 (± 25)
5Ba	18 (± 6.4)	12 (± 5.0)	15 (± 6.7)	16 (± 5.8)
5Ca	23 (± 9.1)	17 (± 6.4)	30 (± 0.95)	50
5Da	34 (± 11.0)	19 (± 5.8)	21 (± 5.3)	50
5Ea	22(± 5.8)	16 (± 2.6)	26 (± 7.2)	52 (± 5.2)
5Fa	21 (± 8.3)	13 (± 2.9)	30 (± 9.5)	33 (± 13.0)
5Ab	20 (± 1.7)	15 (± 0.55)	21 (± 1.5)	24 (± 9.7)
5Ac	26 (± 17.0)	16 (± 3.4)	28 (± 7.7)	50
5Ad	8.6 (± 2.2)	11 (± 5.9)	19 (± 7.6)	32 (± 5.6)
5Ae	1.8 (± 0.19)	4.5 (± 0.018)	7.4 (± 3.9)	27 (± 11)
5Af	2.1 (± 0.19)	2 (± 0.64)	9.6 (± 2.1)	18 (± 6.3)
5Gb	14 (± 3.2)	3.6 (± 1.7)	7.6 (± 1.9)	18 (± 2.8)
5Gc	26 (± 17)	16 (± 3.4)	28 (± 7.7)	50

[a] Data were collected after 48 h of exposure to the drugs. Values are given in μM (between brackets

Chapter 2

Revision of the Asymmetric Organocatalytic Vinylogous-Mukaiyama-Type Reactions

2.1. Aldol reaction

The aldol reaction is one of the most versatile methods in organic synthesis that gives access to β-hydroxy carbonyl compounds, also known as aldol derivatives, through C-C bond formation starting from two carbonyl compounds under basic or acidic conditions.[1] However, the reaction is often accompanied by undesired side reactions such as dehydration, self-condensation and poly-condensation. These limitations, coupled with the abundance of the β-hydroxy carbonyl moiety in natural products or biologically active molecules, have prompted a search for convenient, efficient and controlled methodologies to complete direct cross-aldol reactions.[2]

In order to circumvent these limitations, Mukaiyama *et al.* reported in 1973 the reaction of silyl enol ethers with ketones or aldehydes in the presence of the Lewis acid titanium tetrachloride at room temperature, which resulted in an innovative aldol reaction (equation a, Scheme 1).[3] Subsequent to his initial report, Mukaiyama developed the vinylogous reaction, using a similar protocol to prepare δ-alkoxy-α,β-unsaturated aldehydes (equation b, Scheme 1).[4]

Later on, Mukaiyama also described the reaction between α,β- unsaturated ketones and silyl enol ethers leading to 1,5-dicarbonyl compounds.[5] This last transformation is frequently called the Mukaiyama–Michael reaction, since it leads to the same products as the traditional Michael reaction (equation c, Scheme 1).

Additionally, Mukaiyama disclosed several carbon-carbon bond forming reactions.[6] For instance, the production of β-hydroxy esters was unveiled, using silyl ketene acetals prepared from α-lithio esters and alkylsilyl halides.[7] He also explored with other non-silylated reagents as nucleophiles, as seen in the directed cross-aldol reaction mediated by boron enolates[8] and by tin (II) enolates,[9] and new organic reactions using titanium tetrachloride as Lewis acid.[10]

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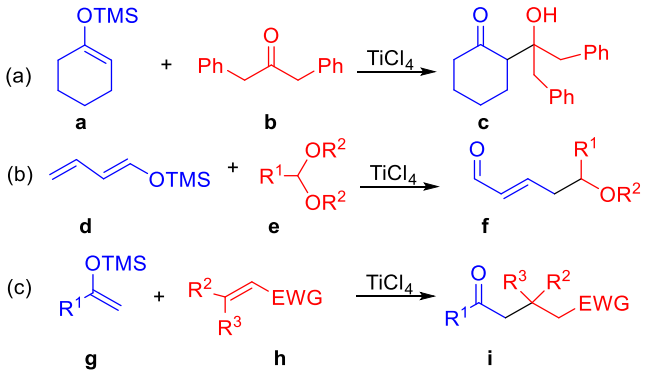
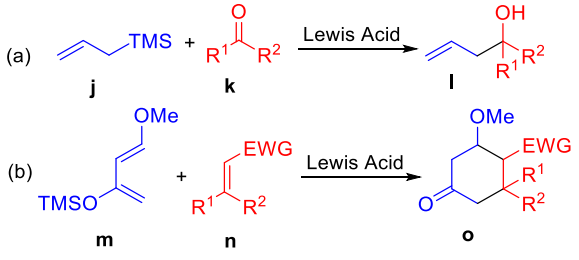
[1] a) R. Mahrwald, *Chem. Rev*, **1999**, *99*, 1095. b) S. Meninno, A. Lattanzi, *Chem. Rec*. **2016**, *16*, 2016.
[2] J. Matsuo, M. Murakami, *Angew. Chem. Int. Ed*. **2013**, *52*, 9109.
[3] T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, *2*, 1011.
[4] T. Mukaiyama, A. Ishida, *Chem. Lett*. **1975**, 319.
[5] K. Narasaka, K. Soai, T. Mukaiyama, *Chem. Lett*, **1974**, 1223.
[6] W. Gati, H. Yamamoto, *Acc. Chem. Res*. **2016**, *49*, 1757.
[7] K. Saigo, M. Osaki, T. Mukaiyama, *Chem. Lett*. **1975**, 989.
[8] a) C. J. Cowden, I. Paterson, *Org. React.* **1997**, *51*, 1. b) T. Mukaiyama, K. Inomata, *J. Am.Chem.Soc.* **1973**, *95*, 967.



Scheme 1. Original and vinylogous Mukaiyama reaction.

The Mukaiyama aldol reaction stimulated the development of a variety of carbon-carbon bond-formation reactions, such as the hetero-Diels-Alder reactions with Danishefsky's diene,[11] and the Hosomi-Sakurai allylation (Scheme 2).[12] Moreover, it fostered the chemistry of Lewis acids in the field of chiral asymmetric synthesis.

The plethora of new transformations pioneered in the 70s and 80s has allowed researchers to develop new concepts and reactivities. The significant challenge of the Mukaiyama reaction resided in the stereocontrol aspect of the process. Therefore, during the 1990s, a large number of asymmetric versions of the previously described reactions were developed using mainly metal- but also free metal-based asymmetric catalytic methods.[13]



Scheme 2. Hosomi-Sakurai allylation and Danishefsky's diene.

[9] K. Inomata, M. Muraki, T. Mukaiyama, *Bull. Chem. Soc. Jpn*. **1973**, *46*, 1807.
[10] T. Mukaiyama, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 817.
[11] S. Danishefsky, J. F. Kerwin Jr., S. Kobayashi, *J. Am. Chem. Soc.* **1982**, *104*, 358.
[12] A. Hosomi, H. Sakurai, *Tetrahedron Lett.* **1976**, *16*, 1295.
[13] a) S. E. Denmark, J. R. Heemstra, Jr, G. L. Beutner, *Angew. Chem. Int. Ed*, **2005**, *44*, 4682. b) E. K. Paul, S. V. Pansare, *Chem. Eur. J*. **2011**, *17*, 8770.

Nowadays, organocatalysis has been established as a new tool for the construction of chiral complex molecules in an easy, fast and economic way, which supposes important advantages for the synthesis of many compounds by chemists.[14] In this introduction, it will be highlighted how chemical researchers have turned their attention to the development of novel organocatalysts in the vinylogous Mukaiyama type reactions.

This introduction will also cover all the publications describing organocatalytic asymmetric Mukaiyama-type processes and their application in the synthesis of important biological molecules. It will be organized by different organocatalytic activation modes, and the diverse organocatalytic systems that have been applied to activate silyldienolate derivatives.

2.2. Organocatalytic Vinyogous Mukaiyama reactions.

On the other hand, the vinylogous term was introduced by Ludwing Claisen in 1926, describing the transmission of electronic effects through a conjugated organic bonding system.[15] Vinylogous reactions occur between the orbitals of the double bond attached to an electron-withdrawing group and an electrophile. Metallodienolates and their silyl counterparts can be described as highly electron rich species. Due to this fact, their reactions are governed by electrostatic interactions, that is, by the total electron density at each carbon atom. For this reason, the different regioselectivity of both metallodienolate and the silyl dienol ethers can be explained by considering the electronic structure of the two reagents.

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[14] a) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed*, **2001**, *40*, 3726. b) D.W.C Macmillan, *Nature*, **2008**, *455*, 304. c) P. Melchiorre, Angew. Chem. Int. Ed. **2009**, *48*, 1360. d) C. M. Marson, Chem. Rev. 2012, 41, 7712. e) J. Wang, B. List, *Science*, **2006**, 1584. f) K. A. Ahrendt, C. J., D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243. g) E. N. Jacobsen, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA*, **2010**, *107*, 20618. h) J. L. Vicario, D. Badia, L. Carrillo, E. Reyes, RSC publishing: Cambridge, 2010. i) B. List, *Chem. Rev*, **2007**, *107*, 5413. j) Y. Quin, L. Zhu, S. Luo, *Chem. Rev.* **2017**, *117*, 9433.

[15] a) C. Schneider, F. Abels, *Org. Biomol.Chem*. **2014,** *12*, 3531. b) X. Jusseau, L. Chabaud, C. Guillou, *Tetrahedron*, **2014**, *70*, 2595. c) I. D. Jurberg, I. Chatterjee, R. Tannert, P. Melchiorre, *Chem. Commun*. **2013**, *49*, 4869.

The frontier-orbital density can be calculated for attack both by electrophiles (electrophilic susceptibility) and nucleophiles (nucleophilic susceptibility). Figure 1 shows the diagrams for both the HOMO orbital coefficients (O.C.) and the electrophilic susceptibility (E.S.) of the lithium dienolate of methyl crotonate and the trimethylsilyl enol ether of methyl 2-propenyl ketone.

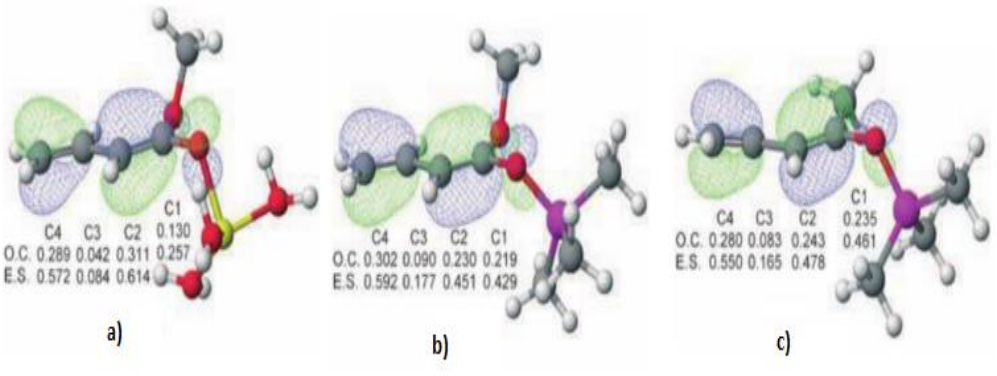


Figure 1. Electronic structures of a) lithium dienolate, b) silyl ketene acetal, c) silyl enol ether.

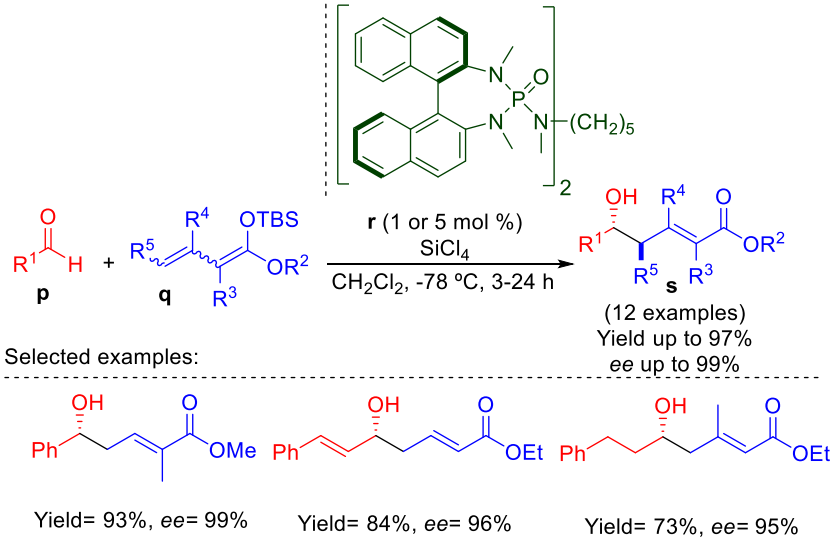
In the case of the lithium dienolate, the HOMO coefficient and the electrophilic susceptibility present higher values at C2 than C4. For this reason, the α-addition is the regioselectivity expected. In the contrary, the silyl dienol ether shows greater HOMO coefficients and electrophilic susceptibilities at C4 rather than C2, foretelling the γ-addition for this substrates. This inherent γ-selectivity of silyl dienol ethers have been reported in different vinylogous Mukaiyama aldol reactions, which have provided an ideal platform for the development of several catalytic enantioselective variants.

2.2.1. Phosphoramides, disulfonimides and phosphonates catalysts.

The first trial of the enantioselective vinylogous aldol reaction catalyzed by chiral *bis*-phosphoramide was described by Denmark and Beutner.[16] The reaction

[16] a) S. E. Denmark, G. L. Beutner, *J. Am. Chem. Soc.* **2003**, *125*, 7800. b) S. E. Denmark, G. L. Beutner, T. Wynn, M. D. Eastgate, *J. Am. Chem. Soc.* **2005**, *127*, 3774.

exclusively affords the γ-addition products with *E* configuration, in the presence of $SiCl_4$ and only 1 mol % of catalyst **r** (Scheme 3). The researchers studied various aldehydes and dienol ethers, obtaining γ-hydroxy enones in good yields and high enantio- and diastereoselectivities. The reactions with aliphatic aldehydes, which are unreactive or led to low *ee*'s, also reacted to obtain high enantioselectivities but it was needed 5 mol % of catalyst for a better yield. In a second related work, the authors examined the reaction with acyclic and cyclic dienolate.[17] The reaction was carried out in higher temperature (-50 ºC) and with addition of *i*-Pr_2NEt and 5 mol % of *bis*-phosphoramide catalyst **r**. All these reactions proceeded with exclusively γ-selectivity and high enantio- and diastereo- selectivity, but the reactions with cyclic dienolate displayed a slightly lower selectivity than acyclic reagent. In these reactions, the studies have shown the lack of reactivity with aliphatic aldehydes.

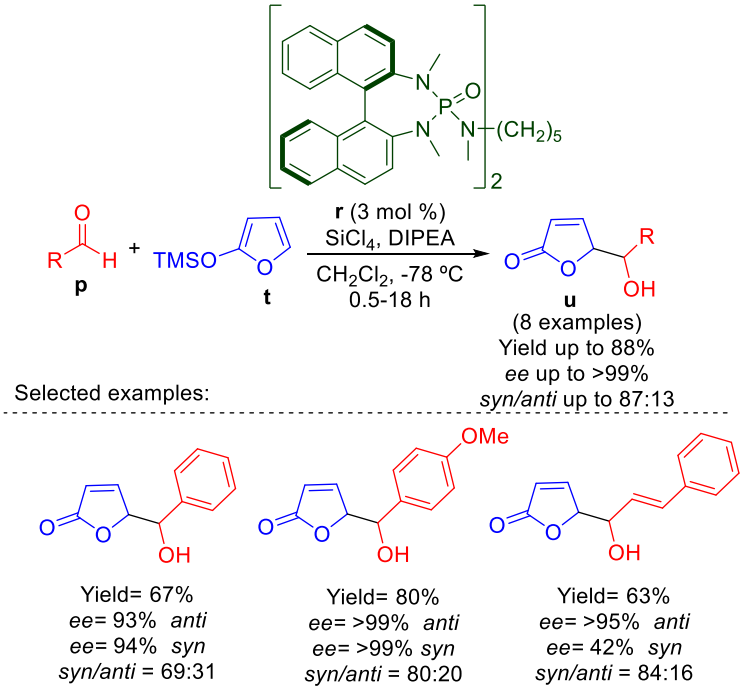


Scheme 3. Vinylogous aldol reaction of ester-derived dienolates **q** and aldehydes **p**.

Palombi *et. al.* described the enantioselective vinylogous aldol γ-addition of 2-trimethylsiloxyfuran **t** to various aldehydes **p**, the best results were obtained with bis-phosphoramide catalyst **r** (Scheme 4).[18] In general, δ-hydroxy butenolides **u** were

[17] S. E. Denmark, J. R. Heemstra Jr, *Synlett*, **2004**, *13*, 2411.
[18] L. Palombi, M. R. Acocella, N. Celenta, A. Massa, R. Villano, A. Scettri, *Tetrahedron: Asymm.* **2006**, *17*, 3300.

obtained with moderate yields and diastereoselectivities, but in most cases high enantioselectivities with aromatic and α,β-unsaturated aldehydes were found. The reported methodology leads to an anti-diastereoselectivity as the major isomer, opposite to the classical method catalyzed Ti (IV) or Sn(IV)-base Lewis acid.[19]



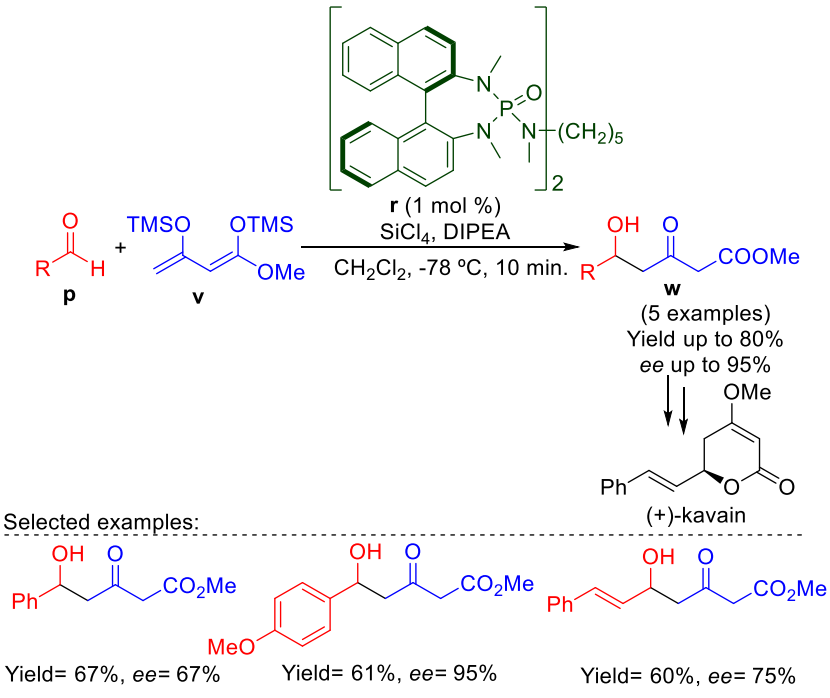
Scheme 4. $SiCl_4$/*bis*-phosphoramide promoted enantioselective vinylogous aldol reaction.

The other example of the application of $SiCl_4$/bis-phosphoramide catalytic system in enantioselective vinylogous aldol reaction is the addition of silyloxydiene **v** to aldehydes **p** (Scheme 5).[20] The reaction was carried out in the same conditions as before, in the presence of only 1 mol % of catalyst **r** and very short reaction time (10 min). The resulting products, δ-hydroxy-β-ketoesters **w**, were obtained in moderate yields and from moderate to high enantioselectivities. There was no information about

[19] a) M. Szlosek, X. Franck, B. Figadere, A. Cave, *J. Org. Chem.* **1998**, *63*, 5169. b) Y. Matsuoka, R. Irie, T. Katsuki, *Chem. Lett.* **2003**, *32*, 584. c) S. Onitsuka, Y. Matsuoka, R. Irie, T. Katsuki, *Chem. Lett.* **2003**, *32*, 974.

[20] R. Villano, R. Acocella, A. Massa, L. Palombi, A. Scettri, *Tetrahedron: Asymmetry* **2006**, *17*, 3332.

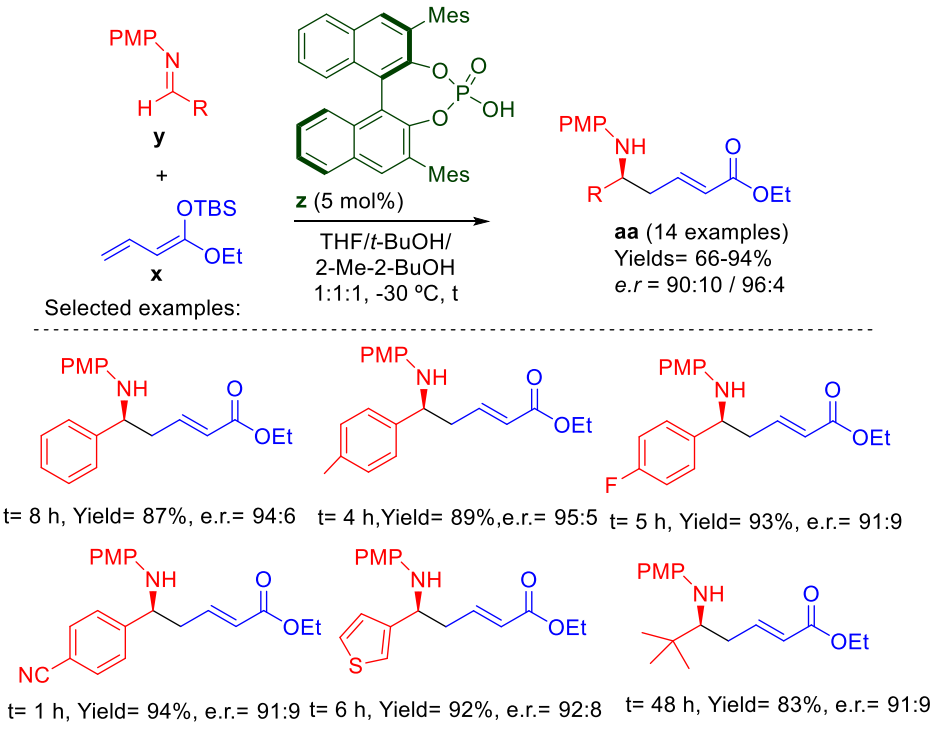
reaction with aliphatic aldehydes. The method was conveniently used for rapid approach to (+)-kavain, a natural bioactive compound.



Scheme 5. The enantioselective vinylogous reaction of silyloxydiene **v** and its application.

In 2008, Schneider *et al.* reported the novel organocatalytic asymmetric vinylogous Mukaiyama-Mannich reaction between acyclic silyl-dienol ethers **x** and *p*-methoxyphenyl imines **y** under BINOL-based phosphoric acid catalysis **z**.[21] The optimal conditions turned out to be 5 mol% of the chiral phosphoric acid, bearing the 3,3´bismesityl groups, a mixture of THF, *t*-BuOH and 2-Me-BuOH as solvent, 1 equiv. of water as additive and the chosen temperature was -30 ºC. These conditions led to the desired γ-regioisomer product **aa** with good yield and enantioselectivity. The reaction tolerates aromatic, heteroaromatic and aliphatic aldimines in good yields and enantiomeric ratios up to 96:4. The authors highlighted also the utility of the methodology by a three-component reaction between the corresponding aldehyde, amine and silyl-dienol ether, obtaining the desired product with a small increase in the yield in comparison with the synthetic imine (Scheme 6).

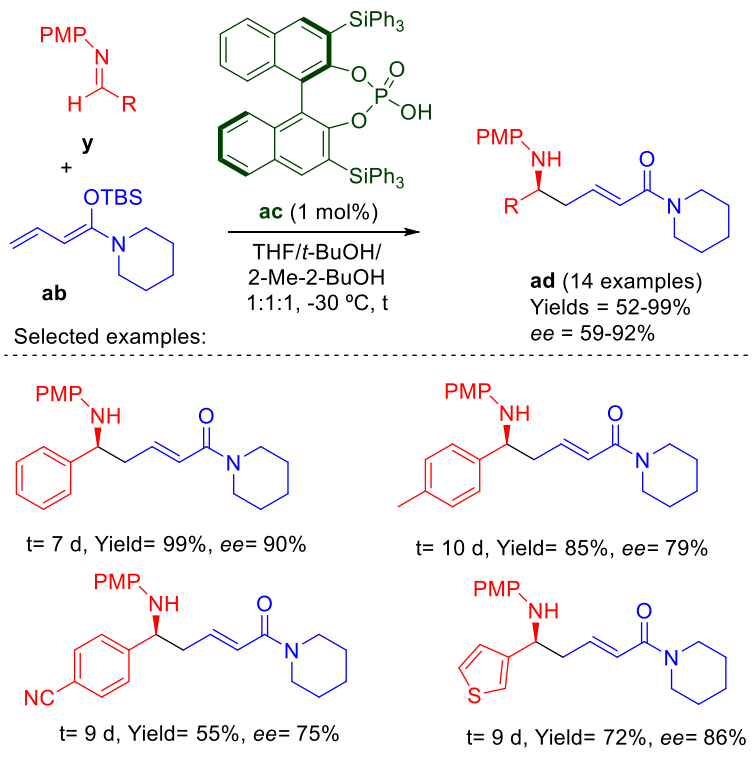
[21] C. Schneider, M. Sickert, *Angew. Chem. Int. Ed*, **2008**, *47*, 3631.



Scheme 6. Asymmetric vinylogous Mukaiyama-Mannich developed by Schneider.

After some months, the same group also published the asymmetric vinylogous Mukaiyama-Mannich reaction of vinyl-ketene silyl N,O acetals **ab** and *p*-methoxyphenyl imines **y**, employing a chiral phosphoric acid **ac**.[22] In this case, 3,3'-bistriphenylsilyl groups were incorporated to the phosphoric acid to obtain better results. The catalytic loading could be decreased until 1 mol%, which led to the desired δ-amino-α,β-unsaturated amines **ad**, in good yields and enantioselectivity after 7 days of reaction. Different vinylketene silyl N,O acetals were studied, obtaining the best results (91% yield, 90% *ee*) with the piperidide vinylketene silyl N,O acetal derivative. Once chosen the best conditions and the nucleophile, the group focused their attention in the scope of the reaction. This tolerates a wide range of different aldimines, giving the desired γ-regioisomer in good yields and enantioselectivities up to 90% (Scheme 7).

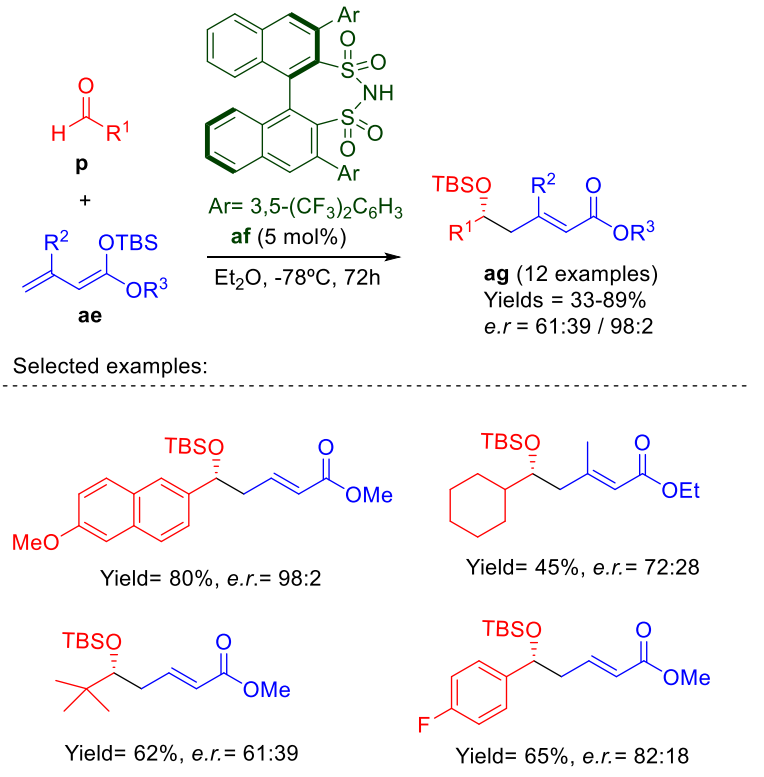
[22] C. Schneider, M. Sickert, D. S Giera, *Org.Lett.* **2008**, *10*, 4259.



Scheme 7. Vinylogous Mukaiyama-Mannich reaction of vinyl-ketene silyl *N,O* acetals **ab** and imines **y**.

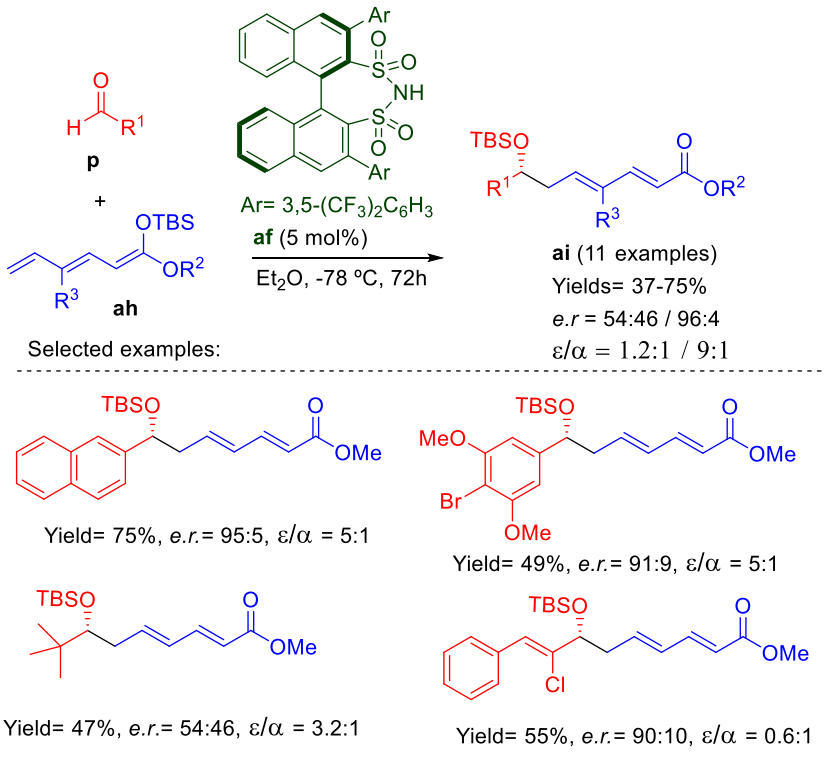
List's group in 2011 described the use of chiral disulfonimide as effective catalysts in the asymmetric vinylogous and bisvinylogous Mukaiyama aldol reactions, obtaining the corresponding aldol products with high regio and enantioselectivities (Scheme 8).[23] The optimal reaction conditions were the use of the silyl-dienol ether **ae** in Et_2O at -78 ºC under 5 mol% of the chiral disulfonimide catalyst **af**. Regarding the scope of this reaction, the group studied different silyl groups at the nucleophile, with few changes on the reactivity. However, in the case of the *tert*-butyl group on the final ester moiety, the yields decreased in comparison with the methyl ester. The reaction tolerated a large number of aromatic groups with EWG and EDGs. The reaction also works with alkyl branched aldehydes, but with lower yields and *ee*'s (Scheme 8).

[23] B. List, M. E. Beck, F. Lay, P. G. Garcia, L. Ratjen, *Angew. Chem. Int. Ed*. **2011**, *50*, 754-758.



Scheme 8. Asymmetric vinylogous and bisvinylogous Mukaiyama aldol reactions.

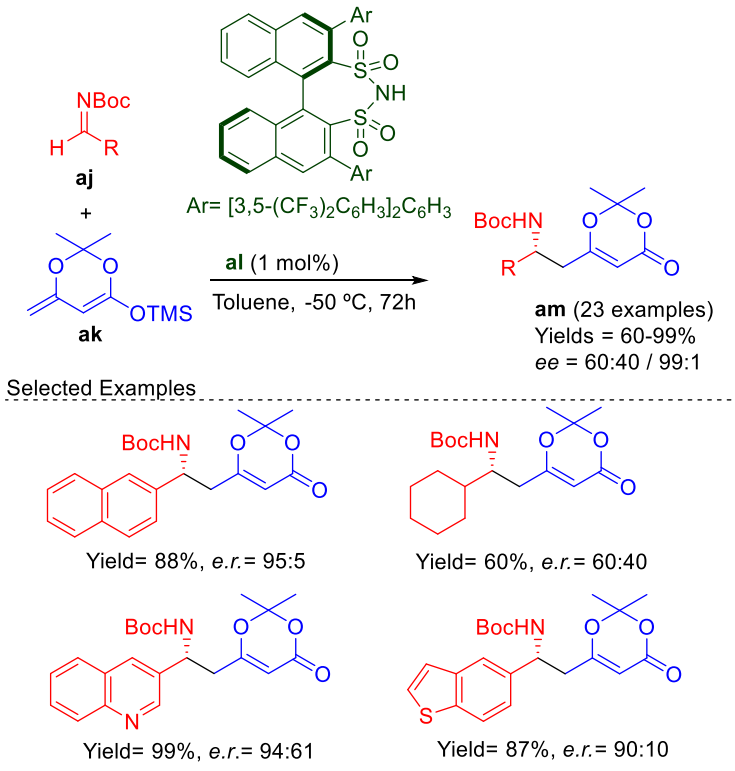
Furthermore, in the same work List group describes the first asymmetric bisvinylogous aldol reaction with aldehydes **p** catalysed by the same chiral disulfonimide **af**. The reaction proceeds with an exclusive ε-regioselectivity. The group studied the scope of the reaction with different aromatic and aliphatic aldehydes, obtaining the desired products with good enantioselectivities and moderate yields (Scheme 9).



Scheme 9. First asymmetric bisvinylogous aldol reaction with aldehydes.

Three years later, List and coworkers published an asymmetric vinylogous Mukaiyama Mannich reaction between *N*-Boc imines **aj** and silyl-dienol ethers **ak** under disulfonimide catalysis, with high yields and *ee*'s (Scheme 10).[24] The optimization of the reaction started with the search of the most effective disulfonimide (1 mol% of **al**), toluene as at -50 ºC. The scope of the reaction allows the use of different aryl and napthyl substituted *N*-Boc imines. Surprisingly, it was observed that the *metha*-methyl-phenyl-*N*-Boc imine present higher enantioselectivity in comparison with the analogous *ortho* and *para* methylphenyl imines derivatives. The reaction was also compatible with halogens groups at the aromatic group of the imine, disubstituted phenyls and heterocyclic *N*-Boc imines with high yields and from moderate to good *ee*'s (Scheme 10). The Mukaiyama-Mannich products **am** were used for further transformations in order to obtain enantiomerically enriched σ-amino-β-ketoesters, very useful in the synthesis of pyperidine and pirrolidine alkaloid derivatives.

[24] B. List, M. V. Gemmeren, Q. Wang, *Angew. Chem. Int. Ed*. **2014**, *53*, 13592.

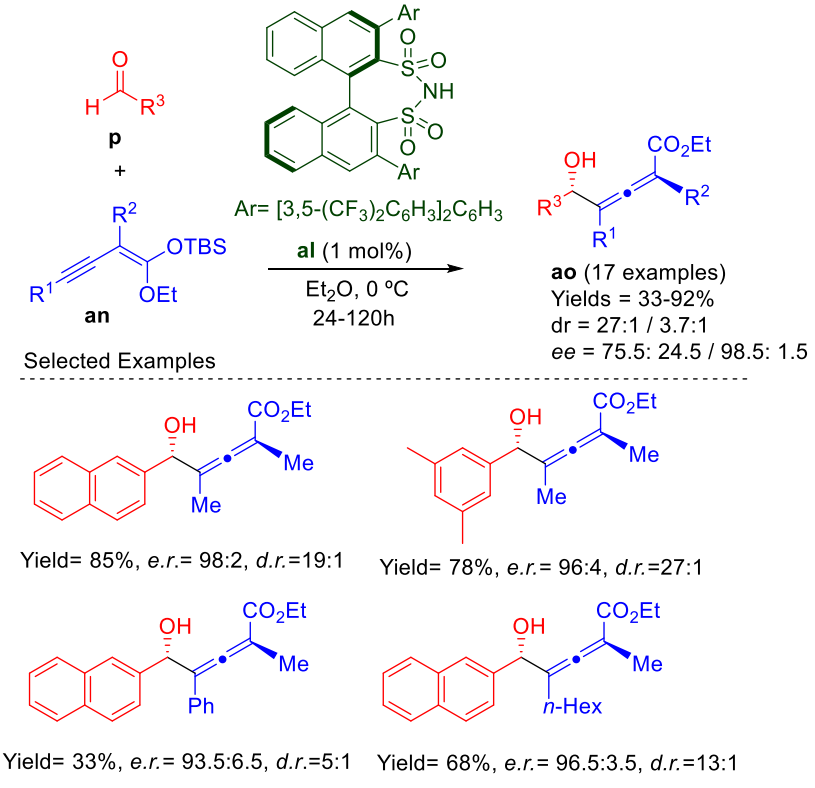


Scheme 10. Asymmetric vinylogous Mukaiyama Mannich reaction between *N*-Boc imines **aj** and silyl-dienol ethers **ak**.

Due to the interesting properties and its versatile reactivity, many research groups have focused their attention on finding new methodologies for the synthesis of chiral allenes. In this regard, List's group published the use of a chiral disulfonimide catalyst in the asymmetric Mukaiyama aldol reaction between alkynyl-substituted ketene acetals **an** and aldehydes **p**, in order to obtain the desired allenes **ao** with high diastero-, enantio-, and complete γ-regioselectivity.[25] The best results were obtained when 5 mol% of the chiral disulfonimide **al** was used and Et_2O as solvent at 0 ºC. The reaction works well with a wide range of aromatic aldehydes. However, the use of the aliphatic aldehydes resulted on the absence of the desired product. Different substitutions at the alkynyl ketene acetals were also studied. A phenyl group at the terminal position resulted on a decrease in the reactivity and selectivity in comparison with a methyl group at the same position. The benzyl group leds to the

[25] B. List, V. N. Wakchaure, A. Blond, A. Tap, *Angew. Chem. Int. Ed.* **2016**, *128*, 9108.

tetrasubstituted allenes **ao** in moderate yields, high *dr* and *ee*'s (Scheme 11). The group demonstrated the value of their methodology by turning the chiral allenes into different valuable substrates such as dihydrofuranes and lactones with good yields and excellent enantioselectivities.



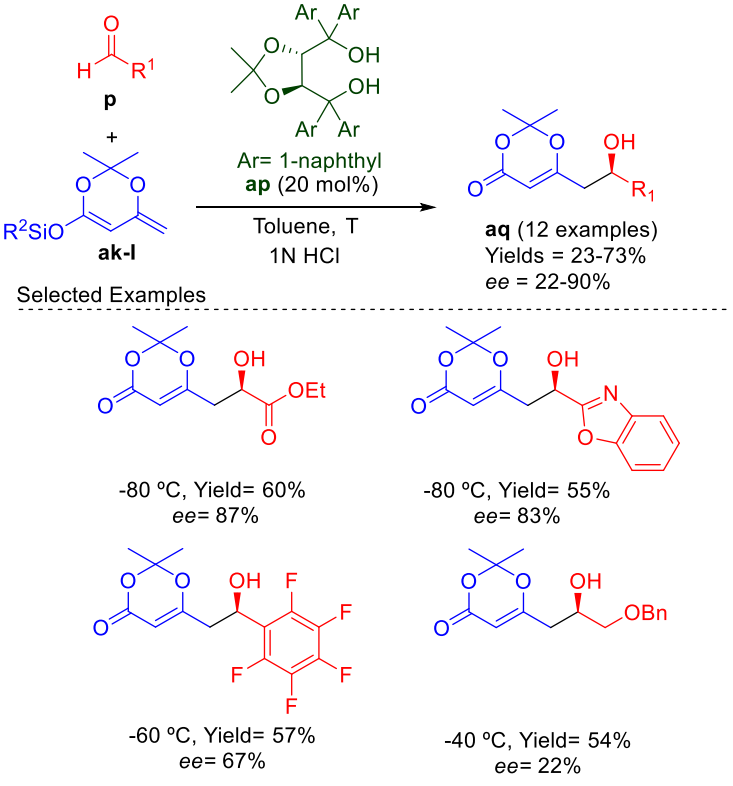
Scheme 11. Asymmetric Mukaiyama aldol reaction between alkynyl-substituted ketene acetals and aldehydes.

2.2.2. TADDOL catalysts

In 2005, Rawal *et al.* described the addition of trialkylsilyldienol ethers to aldehydes under hydrogen bond catalysis.[26] For this work, different chiral alkaloids and diols were studied as catalysts in the reaction of trimethylsilyldienol ether of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**ak-I**) and 2-nitrobenzaldehyde (**p**), obtaining the best results with TADDOL type catalysts. The optimization of the reaction conditions

[26] V. H. Rawal, M. Gravel, V. B. Gondi, *Org. Lett*, **2005**, *7*, 5657.

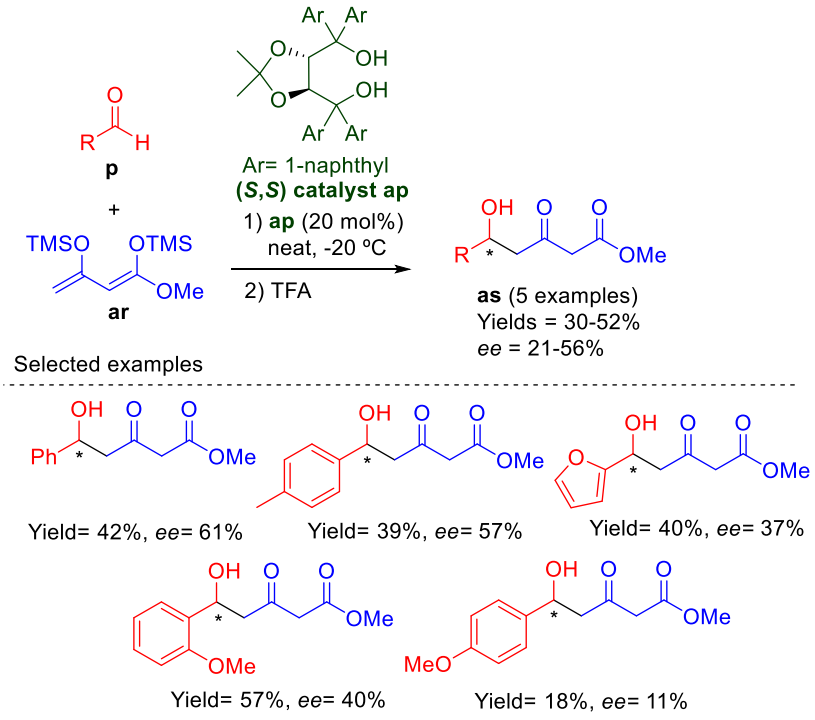
started with the employment of the commercially available 1-napthyl-TADDOL as the catalyst and ethyl glioxalate as the chosen aldehyde. The best *ee*'s results (87% *ee*) were found when the temperature was decreased upon -80 ºC and the TMS group of the nucleophile was replaced by a TBS group. The reaction is compatible with aldehydes such as glyoxalate, α,β-unsaturated, oxazole, thiazole and also with electron poor aromatic rings. The vinylogous aldol products **aq** were obtained with moderate yields and from moderate to good *ee*'s. In all cases only γ-selectivity was observed (Scheme 12).



Scheme 12. Addition of trialkylsilyldienol ethers **ak-I** to aldehydes **p** under TADOOL catalysis.

In 2007, Scettri and co-workers published the vinylogous aldol reaction between aromatic aldehydes **p** and Chan's diene **ar** catalysed by a TADDOL derivative (*S*,*S*-**ap**).[27] It was already known in metal catalysis that Chan's and Brassard's dienes have presented different reactivities in the presence of aldehydes, leading to chiral polyketide derivatives in the case of Chan's diene or to a hetero-Diels-Alder products when Brassard's diene was involved. With all these precedents on mind, Scettri's group decided to study the reaction between Chan's diene and benzaldehyde under the *S*,*S*-**ap** catalysis. Only the corresponding vinylogous aldol product **as** was observed with moderate yield and enantioselecivity. The scope of the reaction included aromatic as well as heteroaromatic aldehydes, obtaining in all the examples vinylogous aldol type products (Scheme 13). However, when the aldehyde contained in its structure an electron withdrawing group (*p*-NO_2, *o*-NO_2), a change in the reactivity was observed, and the reaction led to a mixture of the vinylogous aldol product and the pyrone with moderate *ee*'s (51-60%). These groups carried out mechanistic investigation and established a model for the TADDOL derivatives.[28] It is highlighted an intramolecular hydrogen bond between the hydroxyl groups of the catalyst. Therefore, an intermolecular hydrogen bond can be formed between a free hydroxy and the oxygen of the aldehyde. The last one lower the LUMO energy, making possible the carbonyl activation. The enantioselectivity is described as a result of a π-π* interaction between the naphthyl core of the catalyst and the carbonyl group of the electron poor aldehyde.

[27] A. Scettri, L. Palombi, A. Massa, M. R. Acocella, R. Villano, *Tetrahedron Lett*. **2007**, *48*, 891.
[28] A. Scetrri, L. Palombi, A. Massa, M. R. Acocella, R. Villano, *Tetrahedron Lett.* **2009**, 65, 5571.



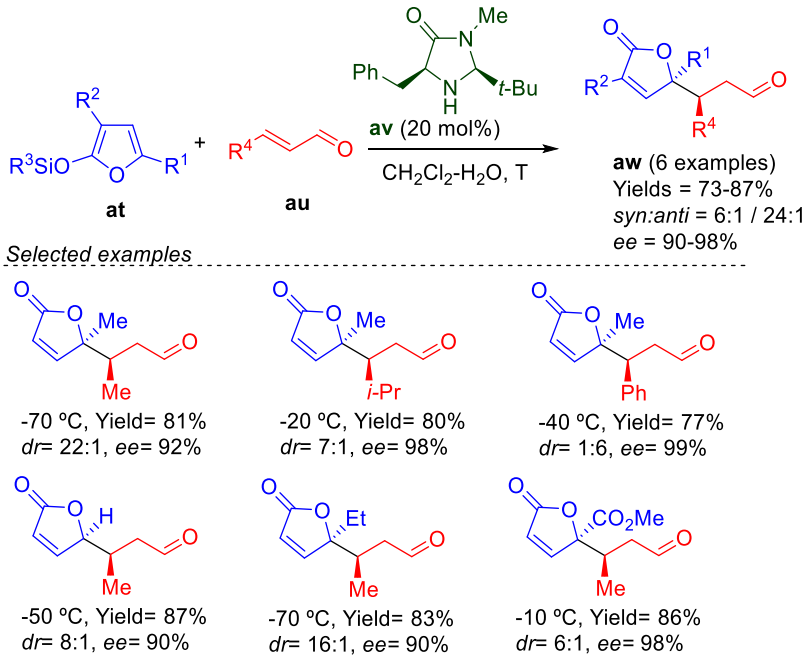
Scheme 13. Vinylogous aldol reaction between aromatic aldehydes **p** and Chan´s diene **ar**.

2.2.3. Pyrrolidines and Imidazolidinones catalyst

Since the MacMillan group reported the use of chiral imidazolidinone as effective catalysts for the 1,4-addition of electron rich aromatic systems to α,β-unsaturated aldehydes, many studies have been made towards finding new chiral catalysts of this type and their applications in carbon-carbon bond formation reactions. In 2003, MacMillan *et al.*, reported the use of chiral imidazolidinone catalysts in the enantioselective Mukaiyama-Michael reaction with α,β-unsaturated aldehydes **au** to obtain γ-butenolide compounds **aw** (Scheme 14) in high yields, diastereo- and enantioselectivities.[29] The best results were obtained by using the amine salt 2,4-dinitrobenzoic acid **av** (DBNA) in a mixture of CH_2Cl_2–H_2O. The presence of water is required to avoid the inhibition of the catalytic cycle by formation of $Me_3SiOSiMe_3$. The reactions work well with aliphatic and aromatic aldehydes, but the diastereoselectivity depends on the aldehyde nature. Therefore, *syn*-isomers were

[29] S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192.

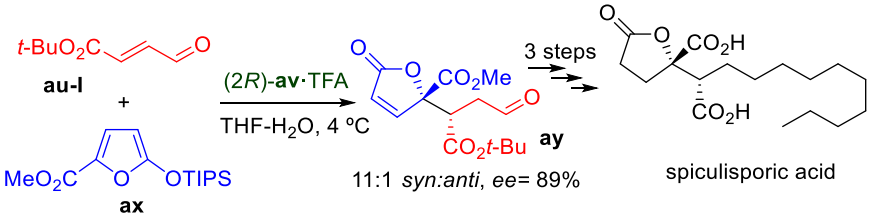
obtained as major compounds when aliphatic aldehydes were used. However, when an aromatic aldehyde was employed (R^3= Ph), the *trans* isomer **aw** was the major diastereoisomer. Moreover, it is remarkable that the change of co-catalyst allows to reverse the diastereoselectivity. Thus, when the reaction was carried out with the methyl (*E*)-4-oxobut-2-enoate, *syn* isomers were obtained with TFA and *trans* isomer with TfOH as cocatalysts.



Scheme 14. Enantioselective Mukaiyama-Michael reaction with α,β-unsaturated aldehydes.

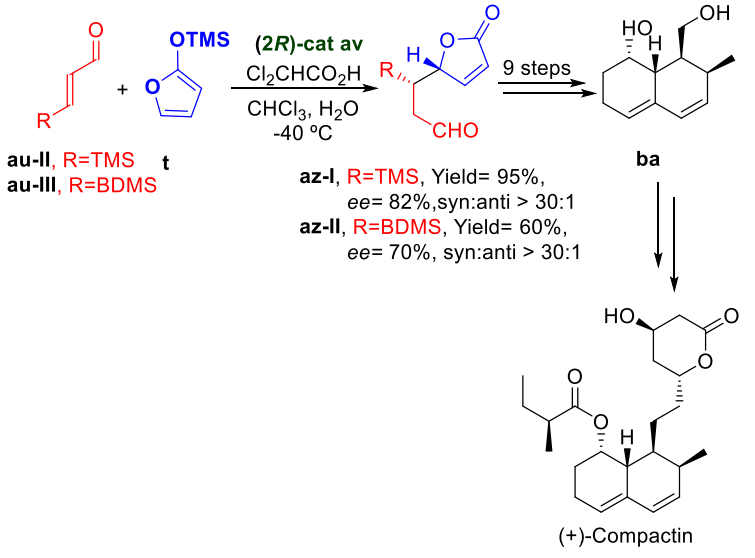
The authors demonstrated the utility of this reaction in the γ-butenolide system construction across the synthesis of the spiculisporic acid (Scheme 15),[30] a *Penicillium spiculisporum* fermentation adduct[31] which is used commercially as a biosurfactant for metal decontamination processes.[32]

[30] S. Brandänge, O. Dahlman, B. Lindqvist, A. Mahlen, L. Mörch, *Acta Chem. Scand. B* **1984**, *B38*, 837.
[31] J. H. Birkinshaw, H. Raistrick, *Biochem. J.* **1934**, *28*, 828.
[32] T. Pekdemir, S. Tokunaga, Y. Ishigami, K. -J. Hong, *J. Surfactants Deterg.* **2000**, *3*, 43.



Scheme 15. Synthesis of the spiculisporic acid.

Later, Robichaud and Tremblay showed the synthesis of butenolides **az** by applying of MacMillan´s organocatalytic Mukaiyama-Michael reaction (Scheme 16).[33] In addition, they showed these diols like the key intermediates for the synthesis of (+)-compactin, which is a metabolite previously isolated from strains *Penicillium brevicompactum*.[34] This work highlights the importance of the steric bulk of the β substituent in the aldehyde to get a good stereoselectivity. Therefore, when a silyl substituent is present at the starting aldehyde, the final δ-butenolide **az** was obtained in good *ee* (82 and 70%) and excellent dr. However, the incorporation of other bulkier substituents as thioether (R = S*t*-Bu or SPh) afforded the desired products albeit with low diastereoselectivities (~3:1).

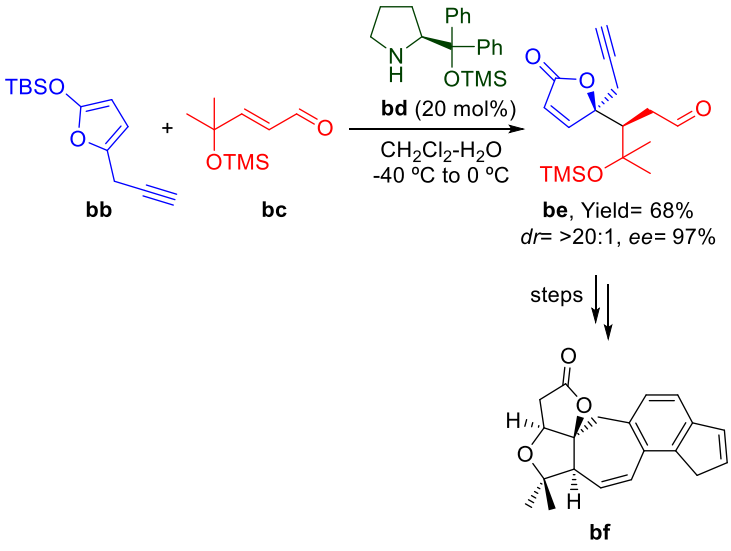


Scheme 16. Synthesis of (+)-compactin.

[33] J. Robichaud, F. Tremblay, *Org. Lett.* **2006**, *8*, 597.

[34] a) A. Endo, M. Kuroda, Y. Tsujita, *J. Antibiot.* **1976**, *29*, 1346. b) A. Endo, M. Kuroda, K. Tanzawa, *FEBS Lett.* **1976**, *72*, 323. c) A. Endo, Y. Tsujita, M. Kuroda, K. Tanzawa, *Eur. J. Biochem.* **1977**, *77*, 31.

Very recently, the Xie group has described the highly stereoselective construction of the C-5-epi ABCDE-ring system **bf** of rubriflordilactone B using an organocatalytic Mukaiyama-Michael reaction as the key step (Scheme 63).[35] The authors carried out a screening of known iminium/enamine type catalysts (proline derivatives and MacMillan catalyst **av**). The best results were achieved with catalyst **bd**. Surprisingly, MacMillan's catalyst (**av**) did not work, perhaps due to its steric hindrance. Nevertheless, the stereochemistry obtained in the Mukaiyama-Michael reaction was appropriate to synthesize the C-5-epi AB-ring system (no epimerization step was necessary).

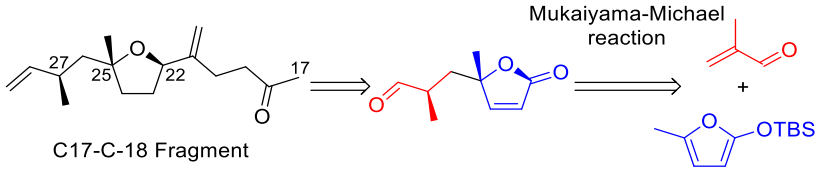


Scheme 17. Synthesis of Rubriflordilactone B **bf** using an organocatalytic Mukaiyama-Michael reaction.

The excellent control of the selectivity at 5 position of γ-butenolide in the Mukaiyama-Michael reaction has been used by Pihko *et al.* to synthetize the C17-C28 fragment of Pectenotoxin-2 (Scheme 18), which bears a thermodynamically unstable "non-anomeric" spiroketal (C-25).[36] In addition, in this reaction must also be generate another estereocenter at C-27. For that purpose, it was necessary to use methacrolein

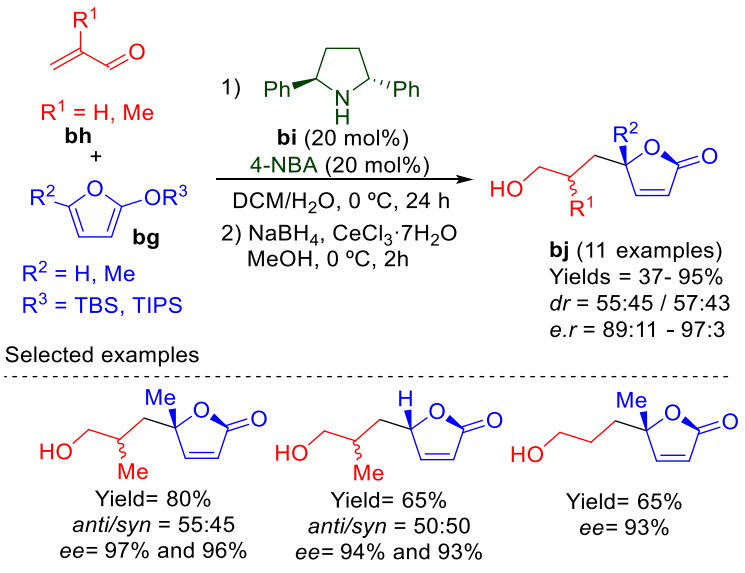
[35] Y. Wang, Z. Li, Z. Xie, Org. Lett. 2016, 18, 792.
[36] E. K. Kemppainen, G. Sahoo, A. Valkonen, P. M. Pihko, *Org. Lett.* **2012**, *14*, 1086.

and to study this process in more detail, because it is a non-common substrate in iminium organocatalysis.



Scheme 18. Synthesis of the fragment C17-C28 of Pectenotoxin-2.

To reach a high level of selectivity with methacrolein, the authors carried out an extensive catalyst screening, evaluating MacMillan's imidazolidinones, prolinol derivatives and a *C2*-symmetric 2,5-diphenylpyrrolidine. The first two options turned in very low enantiomeric excesses and diastereoselectivities (Scheme 65). However, when the *C2*-symmetric 2,5-diphenylpyrrolidine catalyst (**bi**) was used, the final Mukaiyama-Michael adduct was obtained in excellent *ee* (93%) but moderate diastereoselectivity (56:44), which indicates that stereochemical control over C-27 is not possible. However, Pihko and co-workers were able to separate both isomers by column chromatography and the *syn* isomer was used to synthesize the C17-C28 fragment of pectenotoxin-2. The authors also studied the reaction of several silyl enol ethers with acrolein and methacrolein. The reaction with both aldehydes afforded the corresponding γ-butenolides in good yields and high enantiomeric excesses, regardless of the presence or absence of a substituent at the silyl enol ether (R^2).

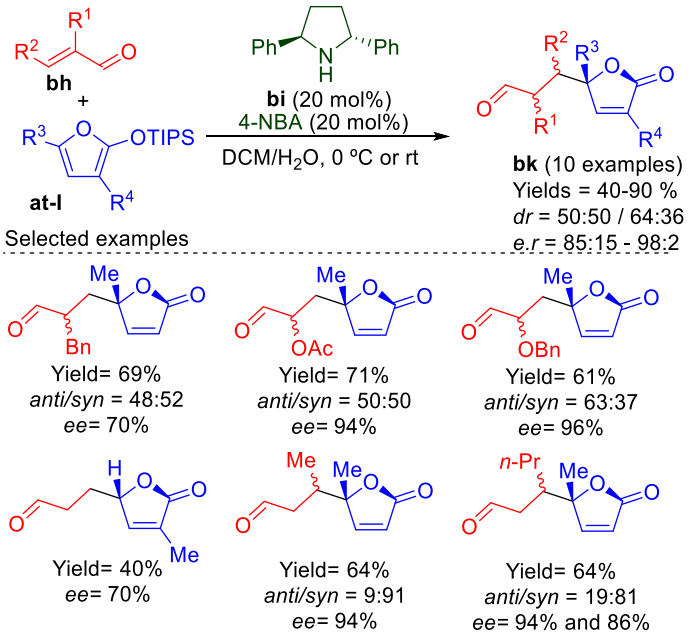


Scheme 19. Mukaiyama-Michael reaction using methacrolein as reagent.

Later, the same research group carried out a detailed study of the reaction conditions (catalyst, silyl protecting group, acid co-catalyst) of the before Michael-Mukaiyama reaction.[37] They determined that the best conditions were the same that in the previous work[38] and increased the reaction scope using other methacroleins and α,β-unsaturated aldehydes **bh** (Scheme 20). The result obtained with methacrolein derivatives were similar to reach before regardless of nature of the substituent. Only, when a benzyl group is present in the starting methacrolein or a 3-methylsilylenol ether is used in the reaction with acrolein, the enantioselectivity decreases until 70%. The reaction also took place with β-substituted acroleins, obtaining good diastereoselectivities (*syn* isomer is the major one) when the silyl enol ether was substituted at C-5. Additionally, the authors carried out a complete theoretical study by means of DFT calculations to rationalize the observed stereoselectivities. Finally, the authors published the protecting group-free total synthesis of (+)-Greek tobacco lactone following their methodology, starting from acrolein and *tert*-

[37] E. K. Kemppainen, G. Sahoo, A. Piisola, A. Hamza, B. Kotai, I. Papai, P. M. Pihko, *Chem. Eur. J.* **2014**, *20*, 5983.
[38] E. K. Kemppainen, G. Sahoo, A. Piisola, A. Valkonen, P. M. Pihko, *Org. Lett.* **2012**, *14*, 1086.

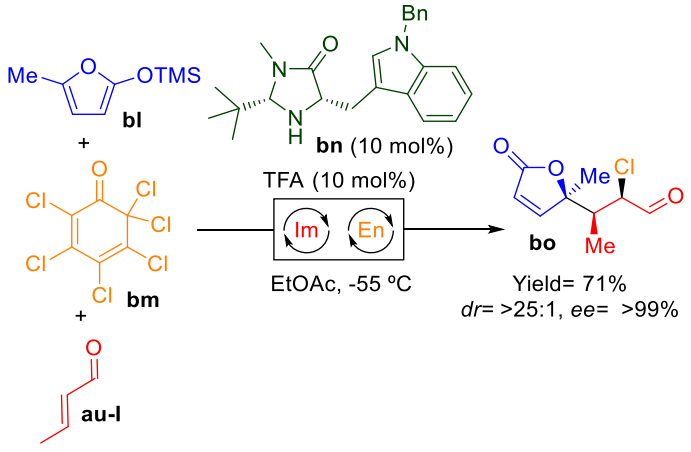
butyldimethyl[(5-methylfuran-2-yl)oxy]silane to afford the natural lactone in four steps with a 34% overall yield.[39]



Scheme 20. Reaction scope with methacroleins and α,β-unsaturated aldehydes.

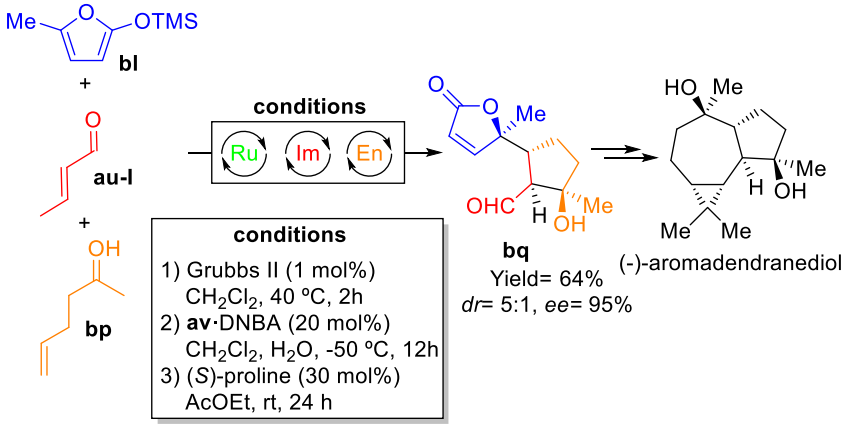
The silyloxyfuran derivative **bl** has also been used in tandem reactions, in which an iminium and an enamine catalytic cycle are involved. MacMillan and coworkers described the reaction of silyloxyfuran **bl** with crotonaldehyde (**au-I**) in the presence of catalyst **bn,** followed by reaction with the chlorinated quinone **bm** to give final difunctionalized aldehydes in α and β positions (Scheme 21).[40] The reaction afforded the corresponding δ-butenolide **bo** in good yield and with complete stereocontrol (only one stereoisomer was obtained).

[39] J. H. Siitonen, P. M. Pihko, *Synlett*, **2014**, *25*, 1888.
[40] Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051.



Scheme 21. Tandem reaction developed by MacMillan using a Mukaiyama reaction.

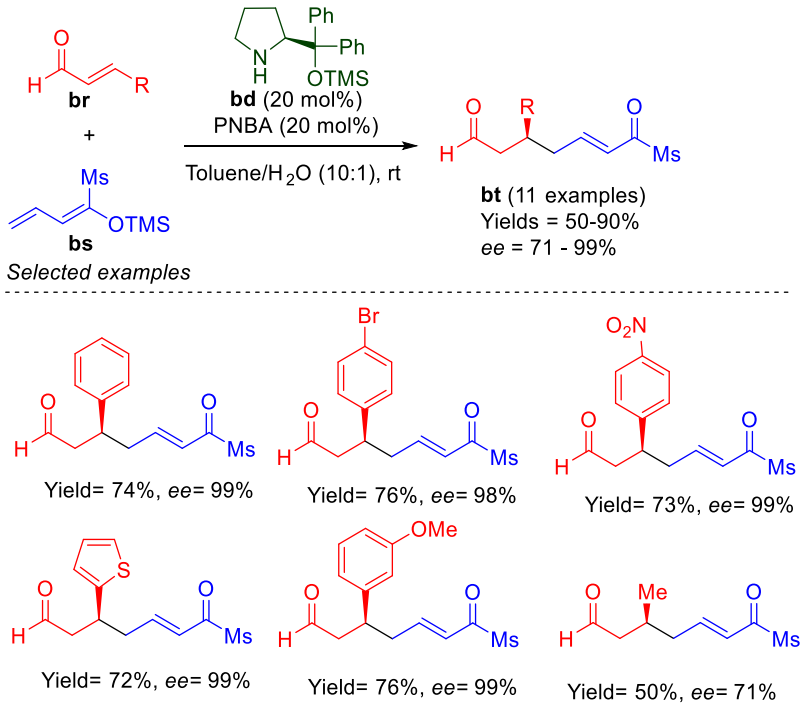
In a related work,[41] MacMillan´s group carried out the synthesis of (-)-aromadendranediol, a sesquiterpene whose bicycle structure presents six stereocenters. For this synthesis, a triple-tandem-catalysis (methatesis/Mukaiyama-Michael/aldol reaction) is developed, where the key step is the Mukaiyama-Michael reaction (Scheme 22).



Scheme 22. Synthesis of (-)-aromadendranediol.

[41] B. Simmons, A. M. Walji, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2009**, *48*, 4349.

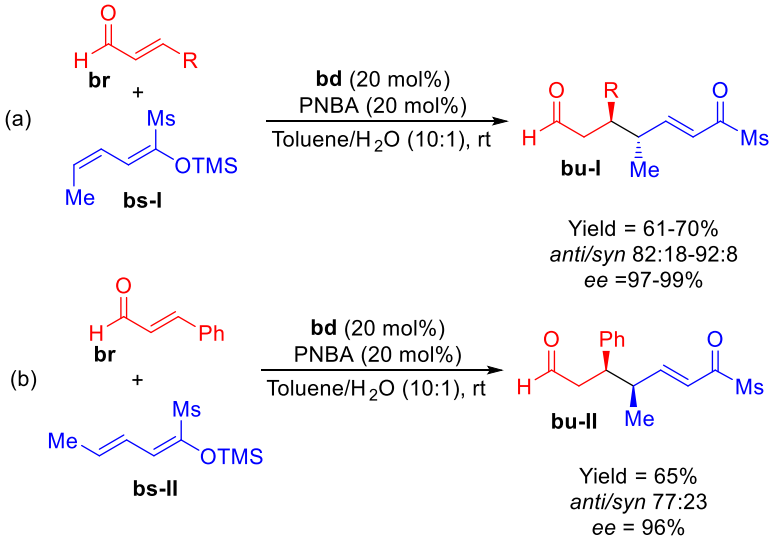
In 2012, Schneider's group reported a new protocol for the synthesis of enantiomerically enriched 1,7-dioxo compounds through a vinylogous Mukaiyama-Michael reaction between acyclic silyl-dienol ethers **bs** and α,β-unsaturated aldehydes **br** under iminium catalysis.[42] The most suitable catalyst for the reaction proved to be the Jørgensen-Hayashi pyrrolidine **bd**. The optimal conditions that leads to the γ-1,4 regioisomers **bt** in good yields and excellent *ee*'s were a combination of a 20 mol% of the Jørgensen-Hayashi catalyst and the same amount of PNBA as co-catalyst. The chosen solvent was a mixture of toluene/water (10:1). When the group carried out the reaction between the acyclic silyl-dienol ether **bs** and cinnamaldehyde under these conditions, they found out the undesired presence of a small amount of the α-1,4 regioisomer. This formation could be avoided by the replacement of the phenyl group in the nucleophile for a mesityl group. The scope of the reaction was studied, employing different type of α,β-unsaturated aldehydes, in all cases with excellent *ee*'s values (Scheme 23).



Scheme 23. Synthesis of enantiomerically enriched 1,7-dioxo compounds **bt**.

[42] V. Gupta, S. Sudhir V., T. Mandal, C. Schneider, *Angew. Chem. Int. Ed*. **2012**, *51*, 12609.

They also studied the effect of the double bond geometry. For this reason, they synthesize the γ-Methyl substituted silyl-dienol ethers **bs-I** and **bs-II** (*Z* and *E* isomers) of the nucleophile and try them in the reaction under the optimal conditions. When *Z*-isomer was used in the reaction, the *anti*-vinylogous Mukaiyama product **bu-I** was formed in 70% yield and 99% *ee*. The diasteroselectivity varies from 82:18 to 92:8 depending on the nature of the used aldehyde. No traces of the α-1,4 isomer was observed (equation a, Scheme 24). However, when the *E*-isomer was presence, the rate of the reaction decreases, obtaining the desired products **bu-II** with moderate yields and diasteroselectivities (equation b, Scheme 24). Consequently, the relative configuration of the major vinylogous Mukaiyama diasteroimer is totally determined by the corresponding configuration of the starting silyl-dienol ether (*Z* or *E* configuration).

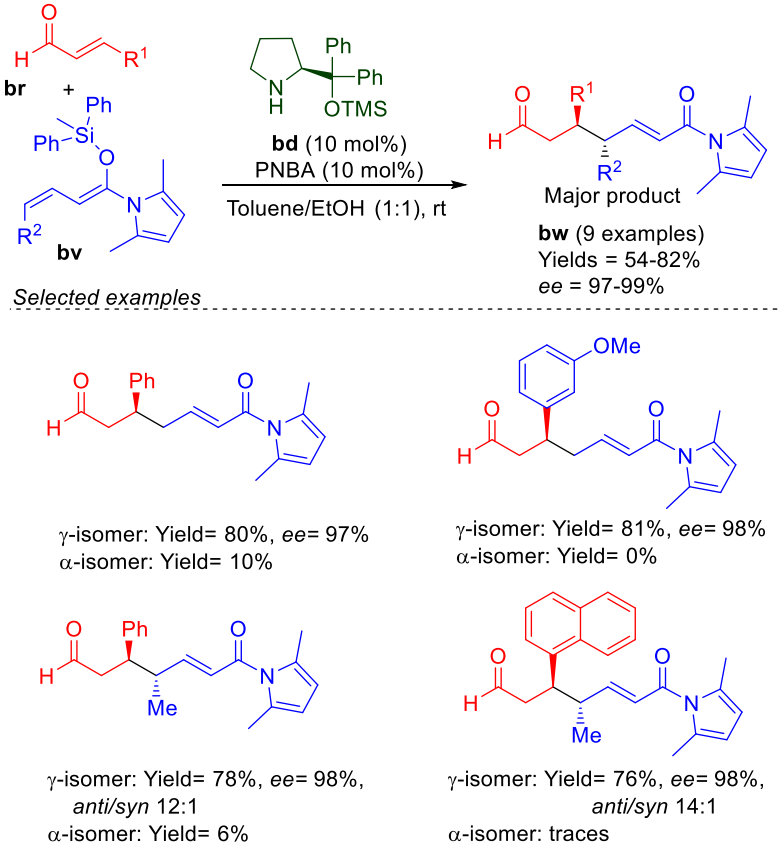


Scheme 24. *Anti*-vinylogous Mukaiyama reaction.

Two years after, the same group published an improved methodology, with a lower catalyst loading and different derivatizations of the final products.[43] In this case, an asymmetric vinylogous Mukaiyama-Michael reaction between the silyl-dienol ether *N*,*O* acetal **bv** and α,β-unsaturated aldehydes **br** under the Jørgensen-Hayashi catalyst **bd** was presented, obtaining the desired product with good yields, excellent *ee*'s and

[43] S. Basu, V. Gupta, J. Nickel, C. Schneider, *Org. Lett.* **2014**, *16*, 274.

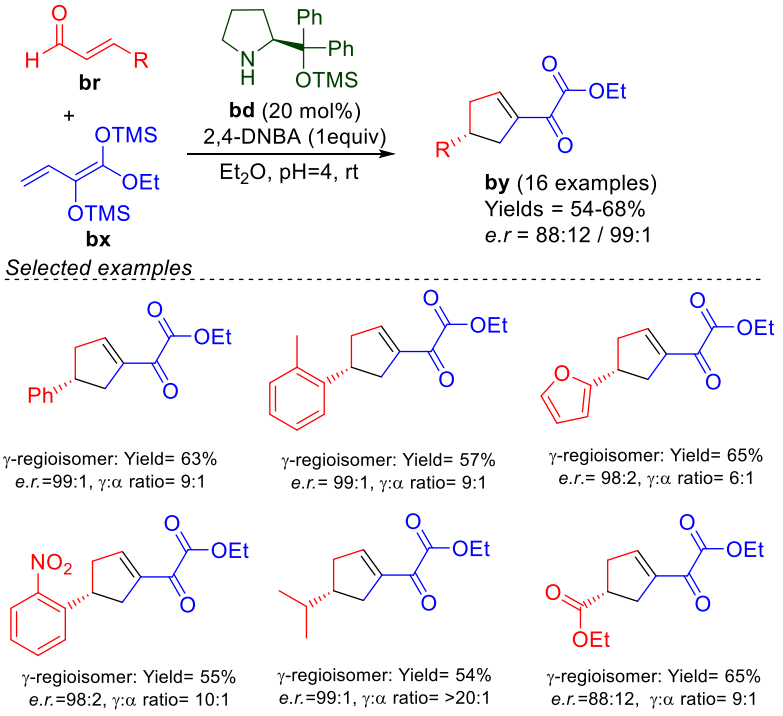
predominantly γ-regioselectivity. The influence of the steric bulk of the silyl group in the regioselectivity was studied, and the best results turned out to be in the presence of the diphenylmethylsilyl (DMPS) dienolate, giving the major product, the γ-regioisomer **bw**, in 80% yield and 98% *ee*. Regarding the scope of the reaction, the protocol was compatible with a wide range of α,β-unsaturated aldehydes and also with γ-methyl-substituted silyl dienol ethers, in general with good yields and excellent *ee*'s (Scheme 25).



Scheme 25. Asymmetric vinylogous Mukaiyama-Michael reaction between the silyl-dienol ether *N,O* acetal **bv** and α,β-unsaturated aldehydes **br**.

In 2015, Schneider´s group reported a new [3+2]-cicloannulation reaction involving the bis-silyl-1,3-dienolate **bx** with α,β-unsaturated aldehydes **br** under pyrrolidine

catalysis (Scheme 26).[44] In this case, it is needed a 20 mol% of Jørgensen-Hayashi catalyst **bd**, and the presence of 1 equivalent of 2,4-dinitrobenzoic acid. The reaction led to the desired product, the γ-regioisomer **by**, with traces of the α-regioselectivity, with good overall yields and excellent enantioselectivities. The reaction tolerates different α,β-unsaturated aldehydes). The cyclopentenyl-α-keto esters could be also derivatized into a wide range of interesting products by simple transformations.



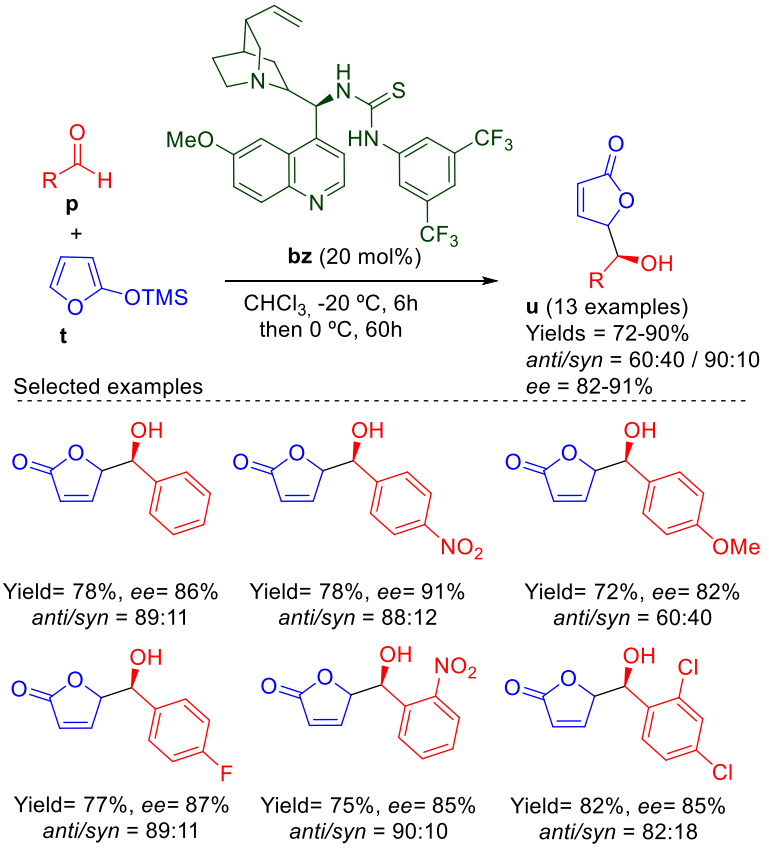
Scheme 26. Cicloannulation reaction involving the bis-silyl-1,3-dienolate **bx** with α,β-unsaturated aldehydes **br** under pyrrolidine catalysis.

2.2.4. Bifunctional Thiourea and Squaramide organocatalyts

In 2010, Wang´s group described the first methodology employing a bifunctional alkaloid thiourea catalyst in the vinylogous Mukaiyama aldol reaction between 2-trimethyl-siloxyfuran **t** and aldehydes **p**.[45] The best results were obtained with 20 mol% of the bifunctional catalyst **bz**, in $CHCl_3$ at -20 ºC for 6 h and then at 0 ºC for

[44] P. R. Nareddy, C. Schneider, *Chem. Commun.* **2015**, *51*. 14797.
[45] N. Zhu, B. –C. Ma, Y. Zhang, W. Wang, *Adv. Synth. Catal*. **2010**, *352*, 1291.

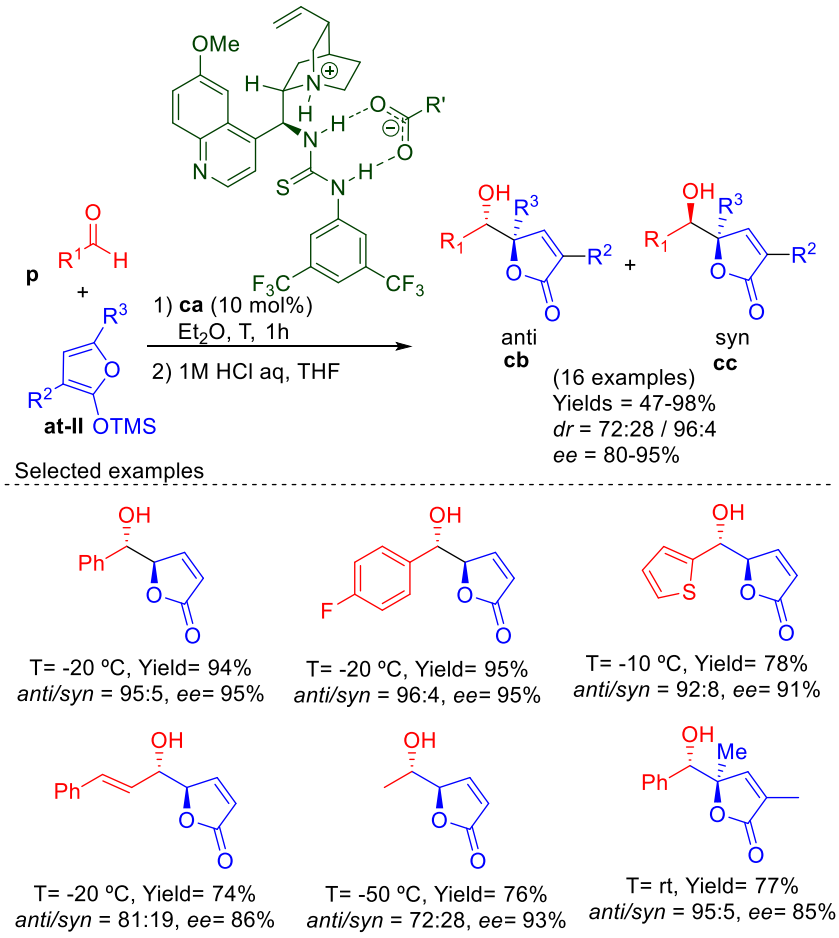
60 h (78% yield, 91% *ee*, 88/12 *dr*). The authors also studied the influence of different additives such as water and alcohols. They found out that in the presence of 10 mol% of water, the yield could increase up to 90%. However, there was a small decrease in the diastero and enantioselectivities. They concluded that a small amount of the additive could transform the TMS species into silanol o silyl ether, regenerating the bifunctional catalyst and increasing the yield (Scheme 27).



Scheme 27. Vinylogous Mukaiyama aldol reaction between 2-trimethyl-siloxyfuran **t** and aldehydes **p**.

Deng's group in 2011 stablished a new synthetic approach for the synthesis of chiral butenolides under the influence of a chiral trifluoroacetic acid derived organic salt **ca** (result from mixing a thiourea amine and a carboxylic acid) (Scheme 28).[46]

[46] R. P. Singh, B. M. Foxman, L. Deng, *J. Am. Chem. Soc.* **2010**, *132*, 9558.



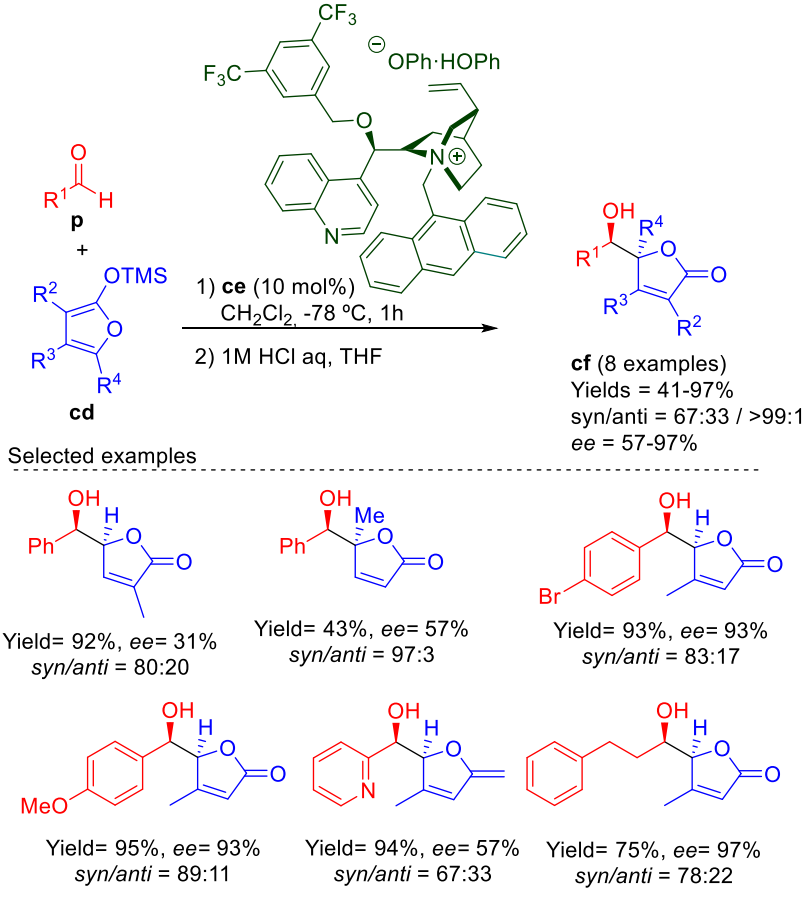
Scheme 28. Synthesis of chiral butenolides under a chiral trifluoroacetic acid derived organic salt **ca**.

2.2.5. Ammonium salt catalyst

Because of their importance as versatile building blocks and their presence in many natural products, many research groups have focused their attention towards the asymmetric synthesis of butenolides. For this reason, in 2007 Mukaiyama's group reported an organocatalitic vinylogous aldol reaction between silyloxy furans **cd** and aldehydes **p** under a chiral ammonium salt catalysis **ce** (Scheme 29).[47] The reaction was firstly studied with benzaldehyde and 2-(trimethylsiloxy)furan in the presence of 10 mol% of the chiral salt. The best results were obtained in CH_2Cl_2 at -78 ºC, with a

[47] H. Nagao, Y. Yamane, T. Mukaiyama, *Chem. Lett*, **2007**, *36*, 8.

moderate enantioselectivity (76% *ee*). The enantioselectivity was improved by changing the substituents of the siloxyfuran. A substitution at 3 or 5 position generates a decrease on the enantioselectivity, whereas a substitution at 4 position increases the *ee*'s up to 93%, with excellent yield and diasteroselectivity (*syn*/*anti* = 93:7). The scope of the reaction was studied with different aliphatic and aromatic aldehydes. In all cases, the desired product **cf** was obtained with good yields and excellent diastereo- and enantioselectivities.



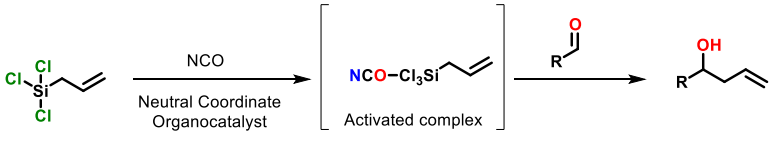
Scheme 29. Organocatalitic vinylogous aldol reaction between silyloxy furans **cd** and aldehydes **p** under a chiral ammonium salt catalysis.

2.3. Main goals of chapters 3 and 4.

In the organocatalytic field, the limited number of activation-methods for the preparation of different and novel asymmetric molecules has long impeded their expansion in organic synthesis. Moderate success has been found for monofunctional catalysts. Hoewever, bifunctional structures lead to promising and efficient asymmetric transformations. Unfortunately, little is known about how bifunctional moieties synergistically work in order to achieve the activation of both nucleophiles and electrophiles. In addition, the limits of reaction landscape catalyzed by these structures are far from being determined.

The most common bifunctional organocatalysts are those based on thiourea and squaramide derivatives.[48] These type of catalysts albeit on its structure a combination of a Brønsted base and a Brønsted acid. Anionic compounds such as fluoride anions and alkoxides are the most used reagents for the activation of silyl compounds, which are usually incompatible with epimerizable chiral centers and others functionalities.[49]

It was in 1993, when Kobayashi first described the concept of a neutral uncharged coordinate organocatalyst (NCO).[50] His group was studying the allylation of aldehydes employing allyltrichlorosilanes in the presence of DMF or HMPA as a solvent without any other promoter. Surprisingly, the reaction proceeded smoothly to afford the corresponding homoallylic alcohols in good yields (Scheme 30).



Scheme 30. Allylation of aldehydes employing allyltrochlorosilanes.

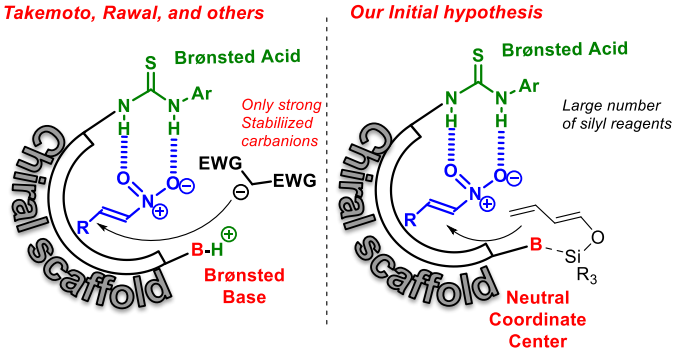
[48] a) M. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc*. **1998**, *120*, 4901. b) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev*. **2009**, *38*, 1187. c) J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc*. **2008**, *130*, 14416. d) J.Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J*. **2011**, *17*, 6890.

[49] H. Nagao, Y. Yamane, T. Mukaiyama, *Chem. Lett.* **2006**, *35*, 1398.

[50] S. Kobayashi, K. Nishio, *Tetrahedron Lett*. **1993**, *34*, 3453.

Several NMR experiments revealed that DMF or HMPA were able to coordinate to the silicon atoms, forming reactive hypervalent silicon intermediates. They concluded that not only DMF or HMPA could promote the allylation of aldehydes, but also N-oxides, sulfoxides, phosphine oxides or amines among others. These molecules act as Lewis bases to activate nucleophiles, but they are uncharged and neutral, so the reactions proceed under neutral conditions. However, this reaction is generally limited to the use of allylsilanes and only an α-attack on C=N and C=O bonds has been achieved.

With all these precedents on mind, we thought to apply this NCO to a bifunctional organocatalyst. This strategy will allow the activation of different electrophiles by the bifunctional catalyst to give the functionalized products together with the regeneration of the bifunctional neutral coordinate organocatalyst. Moreover, the development of these processes could provide access to the unknown reactivity of these silyl reagents (Scheme 31).

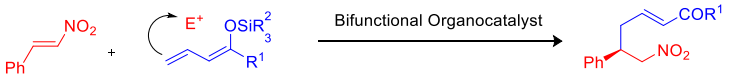


Scheme 31. Comparison of the two activation modes of bifunctional catalysts.

For this reason, the main goal of this part is the study of the activation of silyl dienol ethers under bifunctional catalysis, with different electrophiles.

This part is divided into two individual chapters:

Chapter 3: In this case, we will use nitrostyrene as the electrophile, because of its versatility in organic synthesis, in order to develop the vinylogous Mukaiyama-Michael reaction. (Scheme 32).



Scheme 32. Initial goal of chapter 3.

Chapter 4: To conclude this thesis, we will study the vinylogous Mukaiyama Mannich reaction in the presence of tosyl imines under bifunctional catalysis (Scheme 33).

Scheme 33. Initial goal of chapter 4.

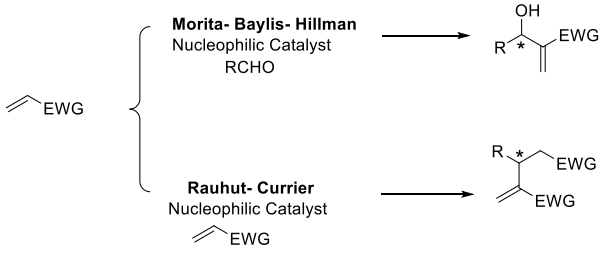
These were initial goals for both projects, but as it will be described in chapters 3 and 4, the obtained results were different to the previous thoughts.

Chapter 3

Asymmetric Synthesis of Rauhut-Currier type Products by a Regioselective Mukaiyama Reaction under Bifunctional Catalysis

3.1. The Rauhut-Currier Reaction.

Carbon-Carbon bond formation is important in organic synthesis for the construction of pharmaceutical products, agrochemicals and materials. In the last decades, many research has been focused on the control of reaction efficiency, stereoselectivity and chemoselectivity. Among the many methods established for the formation of a new Csp^2-Csp^3 bond, it should be highlighted the Morita-Baylis-Hillman[1] (MBH) and the Rauhut-Currier (RC) reactions[2] (Scheme 1).



Scheme 1. Comparison the MBH with the RC.

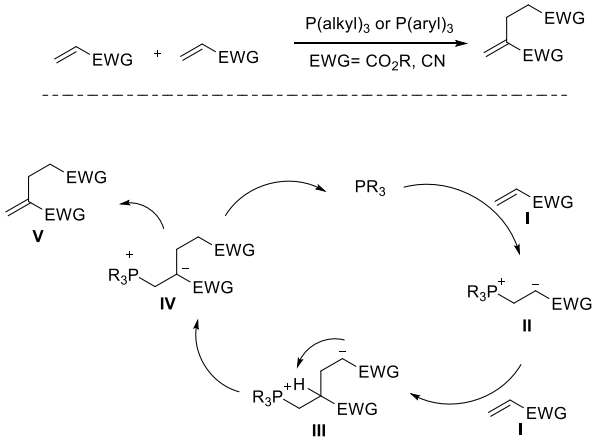
The Morita-Baylis-Hillman reaction is an efficient strategy for the α-functionalisation of activated alkenes with different electrophiles such as aldehydes or imines (aza-Morita-Baylis-Hillman) under the catalysis of an amine or phosphine organocatalyst.[3] On the other hand, the Rauhut-Currier reaction, also well known as the vinylogous Morita-Baylis-Hillman reaction, involves the coupling of an activated alkene or latent enolate, to a second Michael acceptor, forming a new C-C bond between the α position of one of the alkenes and the β position of the other one.

[1] For reviews on MBH see: a) P. Xie, Y. Huang, *Org. Biomol. Chem*., **2015**, *13*, 8578. b) Y. Wei, M. Shi, *Chem. Rev*., **2013**, *113*, 6659. c) D. Basavaiah, P. D. Rao, R. S. Hyma, *Tetrahedron*, **1996**, *52*, 8001. d) S. E. Drewes, G. H. P. Roo, *Tetrahedron*, **1998**, *44*, 4653. e) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811. f) Y. L. Shi, M. Shi, *Eur. J. Org. Chem*, **2007**, *18*, 2905. g) Y. Iwabuchi, S. J. Hatakeyama, *Synth. Org. Chem. Japan*, **2002**, *60*, 2.

[2] For reviews on RC see: a) C. E. Aroyan, A. Dermenci, S. Miller, *Tetrahedron*, **2009**, *65*, 4069. b) K. C. Bharadwaj, *RSC Adv*., **2015**, *5*, 75923. c) K. Y. Lee, S. Gowrisankar, J. Kim, *Bull. Korean Chem. Soc*. **2005**, *26*, 1481. d) G. Masson, C. Housseman, J. Zhu, *Angew. Chem. Int. Ed*. **2007**, *46*, 4614.

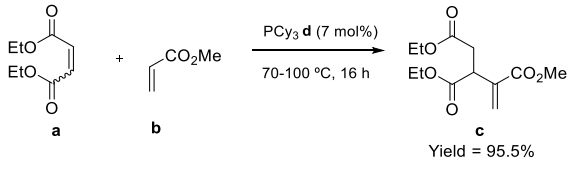
[3] K. Morita, Japan Patent 6803364, *transChem. Abstr*., **1968**, *69*, 58828s.

It was in 1963 when Rauhut and Currier described the dimerization between acrylonitrile and ethyl acrylate under the presence of a phospine catalyst.[4] Authors believed that the reaction took place under the influence of a nucleophilic catalyst, either trialkylphosphine or triarylphosphine (Scheme 2). The first step is the conjugate addition of the catalyst to the activated alkene, leading to the zwiterionic species **II**. Then, a Michael reaction between the enolate and a second alkene generates the intermediate **III**, which undergoes a proton shift, forming intermediate **IV**. The elimination of the phosphine drives to the desired final coupling product **V** (Scheme 2).



Scheme 2. Proposed mechanism for the RC reaction.

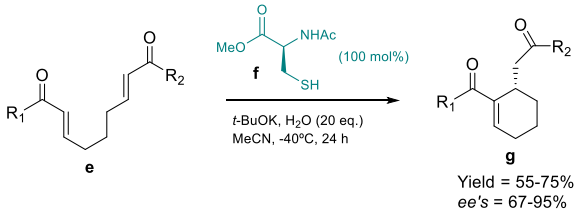
In 1969, Morita and Kobayashi published for the first time a cross coupling reaction between methyl acrilates and fumaric esters, catalysed by triciclohexylphosphine.[5] After 16 hours of reaction, the addition product **c** was obtained with excellent yields (Scheme 3).



Scheme 3. First cross coupling RC.

[4] M. M. Rauhut, H. Currier, *Chem.Abstr*. **1963**, *58*, 11224.
[5] K. Morita, T. Kobayashi, *T. Bull. Chem. Soc. Jpn*, **1969**, *42*, 2732.

During the following 15 years, a wide range of different works were reported related to amine-based catalysts.[6] However, there were no examples of the enantioselective version of the reaction until 2007, when Miller's group described the first enantioselective intramolecular Rauhut-Currier reaction, employing a cysteine derivative as the efficient catalyst (Scheme 4).[7] In this work, it was described that the catalyst can be used for the cicloisomerization of both symmetrical (R_1=R_2) and unsymetrical bisenones (R_2≠R_1) in the presence of potassium *tert*-butoxide and water. The desired products **g** were obtained with moderate yields and excellent enantioselectivities.



Scheme 4. First enantioselective intramolecular RC.

In the following lines we are going to describe some of the most relevant asymmetric examples of the Rauhut-Currier Reaction.[8]

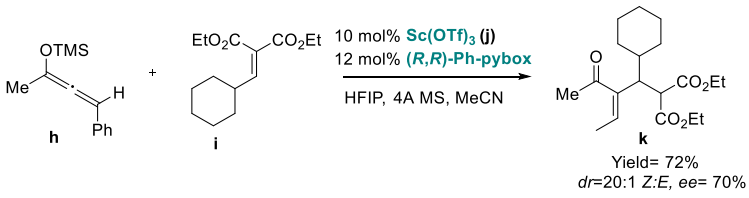
In 2008, Scheidt's group developed the first intermolecular asymmetric RC reaction.[9] They developed a methodology involving silyloxyallenes and malonates derivatives under Lewis acid catalysis. The RC products **k** were isolated with moderate yields and moderate enantioselectivities (Scheme 5).

[6] See for example: a) H. Amri, J. Villieras, *Tetrahedron Lett.* **1986**, *27*, 4307. b) D. Basavaiah, V. Gowriswari, T. Barathi, *Tetrahedron Lett*. **1987**, *28*, 4591. c) S. Drewes, N. Emshe, N. Karodia, Synth.Commun. **1990**, *20*, 1915.

[7] C. Aroyan, S. J. Miller, *J. Am. Chem. Soc*, **2007**, *129*, 256.

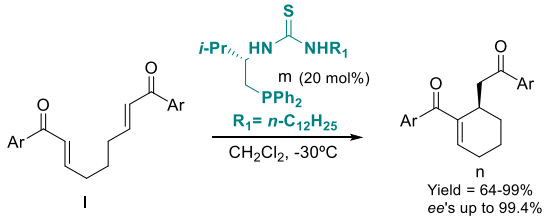
[8] For more details see other works: a) F. Seidel, J. A. Gladysz, *Synlett*, **2007**, 986. b) E. Marques-Lopez, R. P. Herrera, T. Marks, D. Konning, R. M. Figuereido, M. Christmann, *Org. Lett*, **2009**, *11*, 4116. c) X. F. Wang, L. Peng, J. An, C. Li, Q. Yang, L. Lu, F. L. Gu, W. J. Xiao, *Chem. Eur. J*. **2011**, *17*, 6484. d) Q. Zhao, C. K. Pei, X. Y. Guan, M. Shi, *Adv. Synth. Catal.* **2011**, *353*, 1973.

[9] T. E. Reynolds, M. S. Binkley, K. A. Scheidt, *Org. Lett*, **2008**, *47*, 4177.



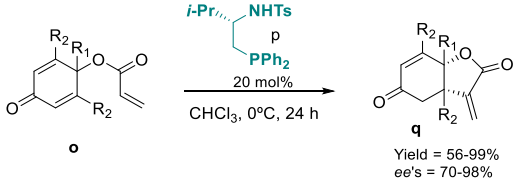
Scheme 5. Asymmetric intermolecular RC catalysed by scandium and pybox ligands.

In 2011, Wu's group published, for the first time, the use of a phosphine-based organocatalyst to promote the intramolecular RC reaction of bis (enones) in good yields and high enantioselectivities (Scheme 6).[10] The authors concluded that both the reactivity and the enantioselectivity were affected by the electronic environment at the enones. The bis (enones) with an electron-withdrawing substituent at the phenyl group were more reactive than those with an electron-donating substituent.



Scheme 6. Intramolecular RC reaction under phosphine organocatalysis.

One year after, Sasai and co-workers reported the desymmetrization of prochiral dienones through a RC reaction, in order to obtain the α-alkylidene-γ-butyrolactone core, which is present in a wide range of natural products (Scheme 7).[11]

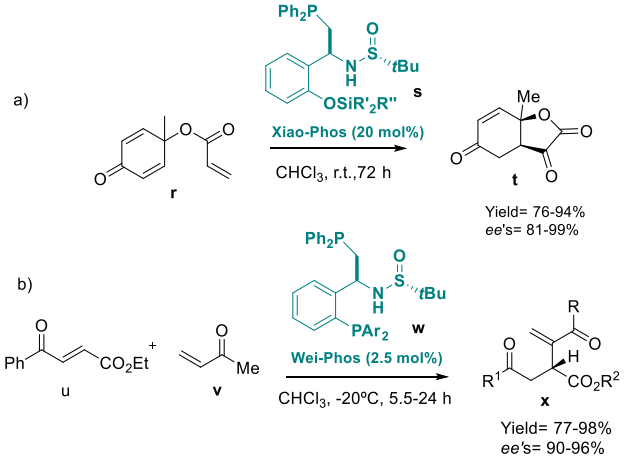


Scheme 7. Synthesis of α-alkylidene-γ-butyrolactones through a RC reaction.

[10] J. Gong, T. Li, K. Pan, X. Wu, *Chem. Commun*., **2011**, *47*, 1491.

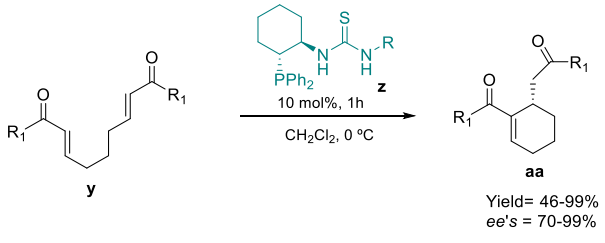
[11] S. Takizawa, T. M. Nguyen, A. Grossmann, D. Enders, H. Sasai, *Angew. Chem. Int. Ed*., **2012**, *51*, 5423.

In 2015, Zhang's group developed two asymmetric RC reactions. The first one involved a novel chiral sulfinamide phosphine (Xiao-Phos) as an efficient catalyst to promote the intramolecular RC reaction with high yields and enantioselectivities (equation a, Scheme 8).[12] The second work highlighted another novel chiral sulfinamide bisphophine catalyst (Wei-Phos) and its application in the asymmetric intermolecular cross-RC reaction between two olefins (equation b, Scheme 8).[13]



Scheme 8. RC reactions under chiral Xiao and Wei-Phos catalysis.

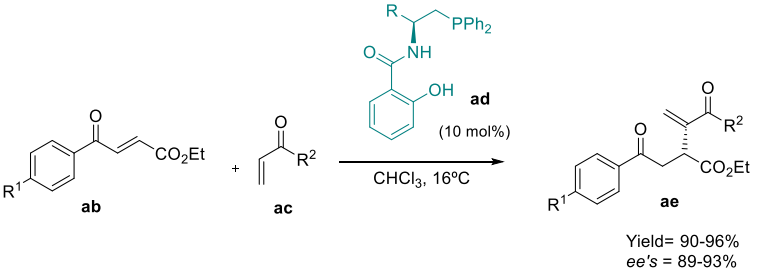
In the same year, Wu and co-workers described another asymmetric intramolecular RC reaction catalysed by a novel thiourea phosphine catalyst.[14] This example is similar to the one reported in 2011, leading to the desired products with excellent yields and enantioselectivities (Scheme 9).



Scheme 9. Asymmetric RC under thiourea phosphine catalysis.

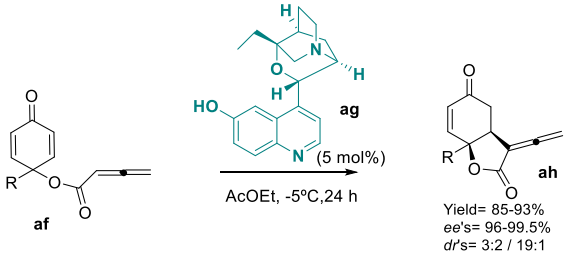
[12] X. Su, W. Zhou, Y. Li, J. Zhang, *Angew. Chem. Int. Ed*, **2015**, *54*, 6874.
[13] W. Zhou, X. Su, M. Tao, C. Zhu, Q. Zhao, J. Zhang, *Angew. Chem. Int. Ed*. **2015**, *54*, 14853.
[14] X. Zhao, J. Gong, K. Yuan, F. Sha, X. Wu, *Tetrahedron Lett*, **2015**, *56*, 2526.

Also in 2015, Huang *et al.* published the intermolecular reaction between aroyl acrylates and methyl vinyl ketones under the influence of a new chiral bifunctional organocatalyst.[15] This organocatalyst, which is the result of the combination of a phosphine, a phenol and an amide, efficiently promotes the reaction, giving the products **ae** with excellent enantioselectivities (Scheme 10).



Scheme 10. Intermolecular reaction of the RC under the catalysis of **ad**.

In 2016, Lu *et. al.* showed an asymmetric intramolecular RC reaction, employing for the first time different allenoates. Authors concluded that the reaction took place under the presence of 1 mol% of β-ICD (**ag**), and the desired products **ah** could be obtained with excellent enantiomeric excesses (Scheme 11).[16]

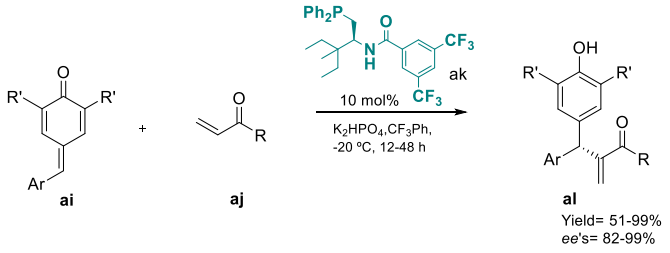


Scheme 11. Enantioselective RC reaction involving allenoates **af**.

At the beginning of this year, Zhang's group described the development of a chiral amide-phosphine bifunctional catalyst **ak**, which was applied to the enantioselective cross-vinylogous RC reaction between alkyl vinyl ketones **aj** and *p*-quinone methides

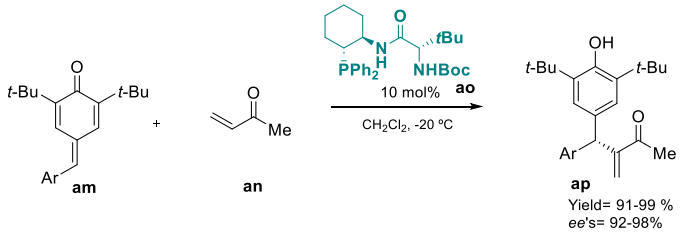
[15] X. Dong, L. Liang, E. Li, Y. Huang, *Angew. Chem. Int. Ed*., **2015**, *54*, 1621.
[16] W. Yao, X. Dou, S.Wen, J. Wu, J. J. Vittal, Y. Lu, *Nat. Commun*. **2016**, *7*, 13024.

ai, furnishing the corresponding products **al** with good yields and high enantioselectivities (Scheme 12).[17]



Scheme 12. Asymmetric Intermolecular Cross Vinylogous RC reaction.

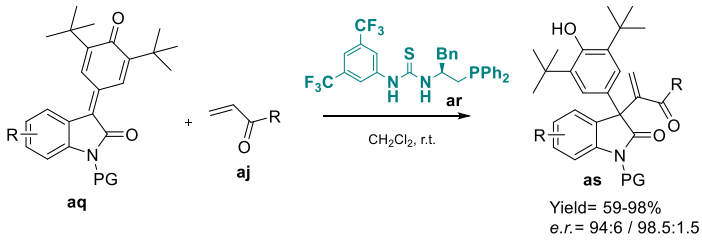
A few months ago, Wu and co-workers described the first RC type 1,6-conjugate addition. The reaction was carried out in the presence of 10 mol% of a phosphine catalyst. The enantioenriched diarylmethine products **ap** were obtained with high yields and *ee*'s up to 98% (Scheme 13).[18]



Scheme 13. Unprecedented RC-type 1,6 conjugate addition.

The last example regarding the RC reaction was individually developed by Tang's group. They revealed an asymmetric cross-RC reaction between vinyl ketones **aj** and *p*-quinone methines **aq** catalyzed by the bifunctional phosphine **ar** (Scheme 14). The desired 3,3 substituted oxindols products were achieved with excellent yields and enantioselectivities.[19]

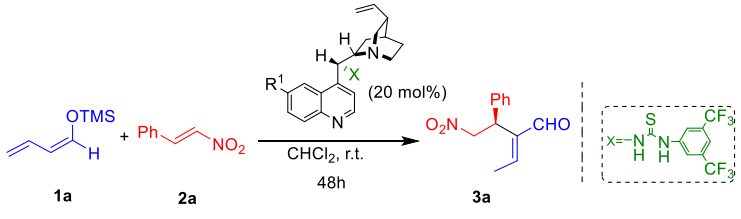
[17] S. Li, Y. Liu, B. Huang, T. Zhou, H. Tao, Y. Xiao, L. Liu, J. Zhang, *ACS Catal*. **2017**, *7*, 2805.
[18] T. Kang, L. Wu, Q. Yu, X. Wu, *Chem. Eur. J*. **2017**, *23*, 6509.
[19] H. Wang, K. Wang, Y. Man, X. Gao, L. Yang, Y. Ren, N. Li, B. Tang, G. Zhao, *Adv. Synth. Catal.* **2017**, *asap*, DOI: 10.1002/adsc.201700649.



Scheme 14. Cross-RC reaction under bifunctional phosphine.

3.2. Proof of Concept and Objectives

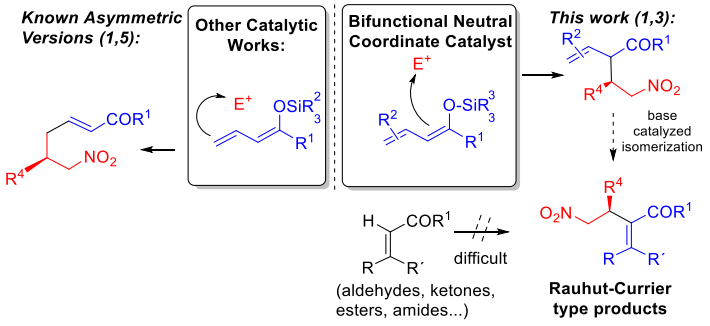
In a first step, we wonder about the behaviour of the silyl-dienol ethers (see description in chapter 2) in the use of bifunctional thiourea and squaramide catalysts. As a proof of concept, we carried out the reaction of the silyl-dienol ether **1a** with nitroalkene **2a** under the catalyst **4a** (Scheme 15). For our delight, we observed a dramatic change in the regioselectivity (only 1, 3 addition was observed), obtaining the aldehyde **3a** with a moderate enantioselectivity (50% *ee*) and 20% of conversion.



Scheme 15. Proof of concept of this chapter.

Driven by this fascinating observation, we realised that our methodology makes possible the obtention of Rauhut-Currier type products **3**, which are excellent building blocks for the synthesis of many complex molecules. Moreover, as we showed in section 3.1, the lack of reactivity of the mono-β-substituted and β,β-disubstituted double bonds makes difficult the synthesis of these enantioenriched tri- and tetra-substituted double bonds with different electrowithdrawing groups in the Rauhut-Currier reaction.

For this reason, we propose as the main goal of this chapter, the development of a general methodology for the addition of silyl dienol ethers to nitroalkenes under bifunctional catalysis, in order to obtain any type of Rauhut-Currier products with high enantioselectivities (Scheme 16).



Scheme 16. Comparison of the usual reactivity of the 1,5-Mukaiyama with the present work.

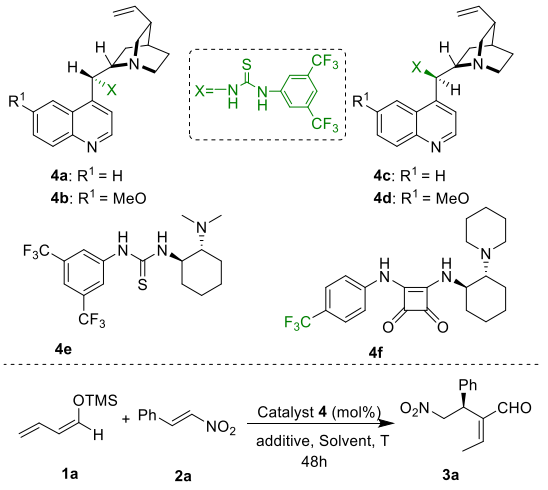
3.3. Results and discussion

3.3.1. Screening of the reaction conditions.

Firstly, different thioureas cinchona catalysts **4a-d** gave similar conversions, in all the cases with moderate yield and enantioselectivities (Entries 1-4, Table 1). Driven by our experience in bifunctional catalysis,[20] we decided to explore the Takemoto's bifunctional thiourea **4e**, but it did not increase the previous results (Entry 5, Table 1). However, 81% of *ee* was achieved in the presence of the Rawal's bifunctional squaramide **4f** (Entry 6, Table 1).

Table 1. Screening of different bifunctional catalysts.

[20] a) C. Jarava-Barrera, F. Esteban, C. Navarro-Ranninger, A. Parra, J. Alemán, *Chem. Commun*., **2013**, *49*, 2001. b) A. Parra, R. Alfaro, L. Marzo, A. Moreno- Carrasco, J. L. García Ruano, J. Alemán, *Chem. Commun*, **2012**, *48*, 9759. c) V. Marcos, J. Alemán, J. L. García Ruano, F. Marini, M. Tiecco, *Org. Lett*. **2011**, *13*, 3052.



Entry	Catalyst (mol%)	Solvent	Ee (%)	Conv.(%)
1	**4a** (20 mol%)	CH_2Cl_2	50	21
2	**4b** (20 mol%)	CH_2Cl_2	67	10
3	**4c** (20 mol%)	CH_2Cl_2	56	30
4	**4d** (20 mol%)	CH_2Cl_2	64	20
5	**4e** (20 mol%)	CH_2Cl_2	56	55
6	**4f** (20 mol%)	CH_2Cl_2	81	48
7	**4f** (20 mol%)	Dry Xylene	-	n.r.
8	**4f** (20 mol%)	THF	96	22
9	**4f** (20 mol%)	DCE	99	63
10	**4f** (20 mol%)	Xylene + H_2O	96	69
11	**4f** (20 mol%)	Toluene+ H_2O	96	88
12	**4f** (20 mol%)	DCE + H_2O	>99	100
13	**4f** (10 mol%)	DCE + H_2O	>99	100 (86)
14	**4f** (5 mol%)	DCE + H_2O	97	53

[a] Conditions: **1** (0.3 mmol), **2** (0.1 mmol), **4f** (20 mol %) in DCM (0.3 mL) at rt and stopped at 48 h. [b] Conversion measured by ^{1}H-NMR. [c] 5 equiv. of H_2O was used as an additive. [d] Isolated yields in paretheses.

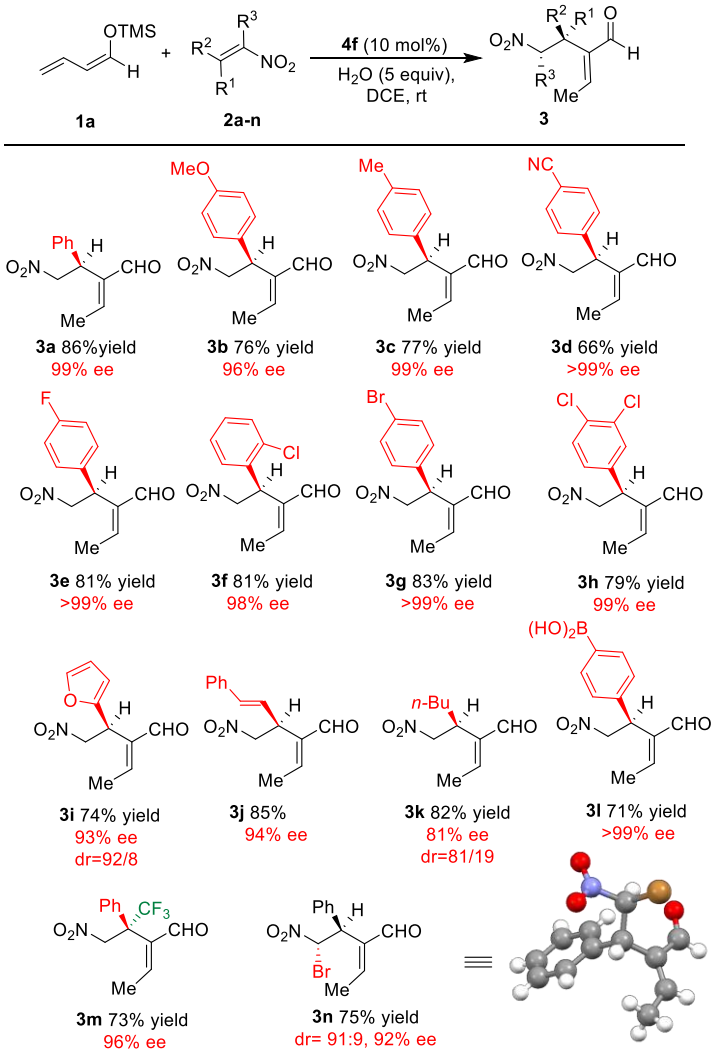
In the next step we explored different solvents under **4f** catalysis. Interestingly, the use of dry xylene did not result in any conversion at all, whereas other bench-solvents, such as THF and DCE, promoted the reaction from low to moderate conversion (entries 7-9, Table 1). However, the addition of 5 equiv. of water (see Experimental part for the water study) increased the conversion (entries 10-12, Table 1), remaining equal to or similar in enantioselectivity. In the case of DCE a conversion of >99 % and >99 % *ee* was
found (entry 12). Then lower catalytic loadings were studied, these also produced a similar result with 10 mol % catalyst **4f** (entry 13) but a 5 mol % provoked a substantial decrease in the final conversion (entry 14, Table 1). The squaramide **4f** showed higher rigidity and increased H-bond distance and canted H-bond angle than thioureas **4b** offering a higher enantioselectivity in this reaction.

3.3.2. Scope of the reaction.

Under these optimized conditions, the scope of the reaction using different substituted nitroalkenes **2** and silyl reagents **1** was carried out (Table 2 and Scheme 17). Different electron donating (*p*-MeO, *p*-Me, **3b**, **3c**) or electron withdrawing groups (*p*-F, *p*-CN, **3d**, **3e**) as well as *ortho*-substituent groups (*o*-Cl, **3f**) at the aryl group of the nitroalkene were tolerated under these conditions. Other synthetically useful halogens such as *p*-Br or, 3,4-dichloro (**3g**, **3h**) were also studied, and also showed excellent enantioselectivies and diastereoselectivities (only one double bond stereoisomer was found in all these cases). Very interestingly, an alkene containing a boronic acid (**2l)**, with acid protons that would interact with the catalytic system, was also compatible, giving the final Rauhut-Currier product **3l** with 99 % *ee* and 71 % yield. Heterocycles, double bonds and alkyl chains (**3i**, **3j**, **3k**) also worked with excellent yields and good *ee*'s in all cases, but with a lower diastereoselectivity for compounds **3i** and **3k**. The more challenging reactions with trisubstituted itroalkenes **2m** and **2n** were also studied. The optically enriched quaternary center product **3m** was obtained with a good yield and excellent enantioselectivity (96 % *ee*), whereas the reaction with **2n** gave the final product **3n** with an excellent *ee* and good diastereocontrol at the bromo position (*dr* = 91:9).

The absolute configuration of the asymmetric center and the configuration of the double bond of **3n** were unequivocally assigned as (*E*, 1*S*, 2*S*) (bottom, Table 2) by X-ray crystallographic analysis.[21] We assigned the same absolute configuration to all the double enals **3** as *E*, 2*S*.

Table 2. Scope of the Rauhut-Currier reaction with different nitroalkenes.



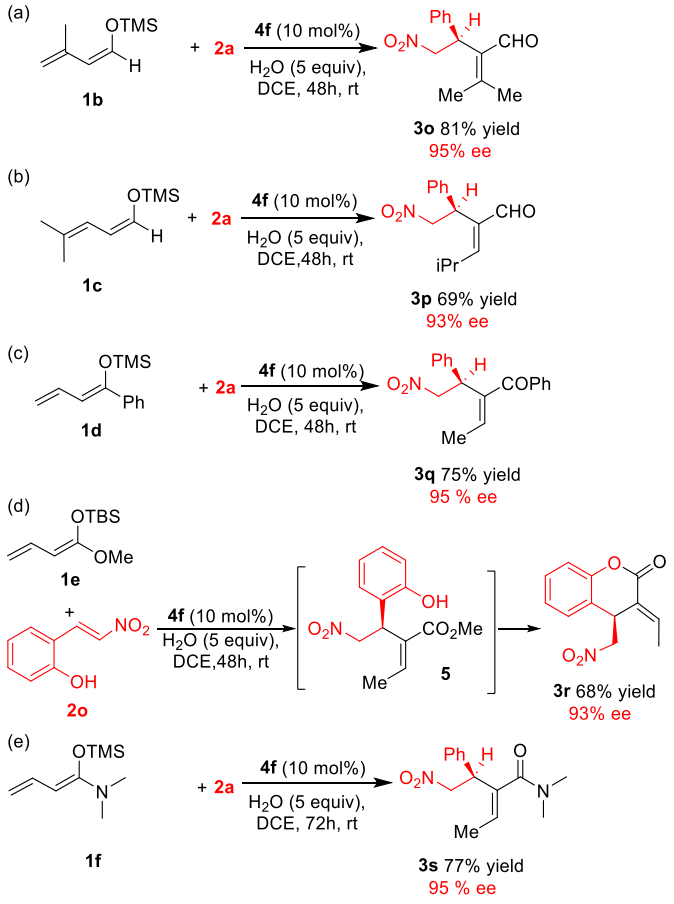
[a] Conditions: **1** (0.3 mmol), **2** (0.1 mmol), **4f** (10 mol %) and H_2O (5 equiv.) in DCE (0.3 mL) at rt for 24-48 h. [b] Conversion measured by ^{1}H-NMR.

[21] CCDC 1471840 (**3n**) contains the crystallographic data.

The substitution at the silyl dienol ether was studied with **1b-f** (Scheme 17). The substitution at the 4 and 5-positions led to the β,β-disubstituted and β-monosubstituted adducts **3o** and **3p** in good yields and enantioselectivies which are not possible to obtain by the reported Rauhut-Currier reactions (equation a and b).[22] In addition, the reaction tolerated different groups in α position to the TMSO group at the silylenolate **1d-f**. Therefore, the phenyl group led to the ketone **3q** with an excellent enantioselectivity (equation c) whereas the silyl reagent **1e** reacted with **2o** to give the intermediate **5**, that spontaneously cyclized under the basic conditions to give the final lactone **3r** with a good ee and yield (equation d). Finally, the synthesis of amides, which cannot be activated under the standard Rauhut-Currier reaction, gave the adduct **3s** in an excellent yield and enantioselectivity (equation e, Scheme 17).

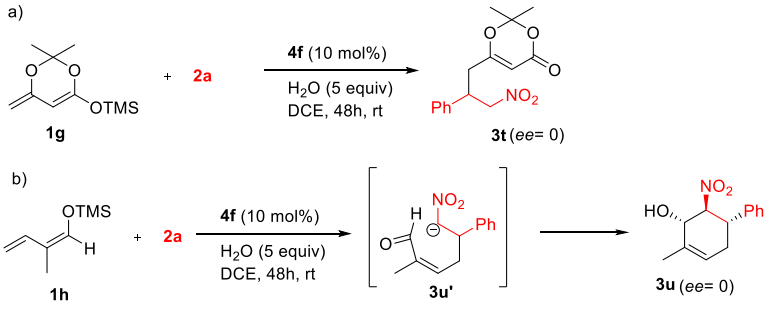
[22] a) X. Dong, L. Liang, E. Li, Y. Huang, *Angew. Chem. Int.Ed.* **2015**, *54*, 1621.b) X. Zhao, J. Gong, K. Yuan, F.Sha, X. Wu, *Tetrahedron Lett*, **2015**, *56*, 2526.

Scheme 17. Scope of the Rauhut-Currier reaction with different silyl dienol ethers.



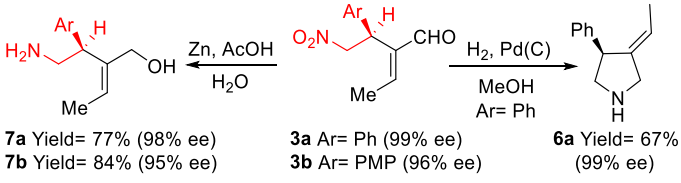
[a] Conditions: **1** (0.3 mmol), **2** (0.1 mmol), **4f** (10 mol %) and H_2O (5 equiv.) in DCE (0.3 mL) at rt for 24-48 h. [b] Conversion measured by ^{1}H-NMR.

Interestingly, we also tried with the nucleophiles (**1g**, **1h**) shown in Scheme 18. The reaction in the case of the cyclic silyl dienol ether **1g** led to the 1,5 functionalization, but with no control in the enantioselectivity (equation a, Scheme 18). Moreover, when a substitution at the C3 position was studied (**1h**), the 1,5-regioisomer was also observed, obtaining the intermediate **3u'**, which evolves into thr cyclic product **3u** with a null enantioselectivity (equation b, Scheme 18).



Scheme 18. Different nucleophiles employed in the reaction.

The Rauhut-Currier products obtained can be selectively reduced to obtain precursors of important aminoacids, which are analogs of important pharmaceutical products.**23** The products **3a**-**3b** were reduced with Zn in an acidic media to produce the aminoalcohols **7a** and **7b** with good enantioselectivity (left, Scheme 19). In addition, the pyrrolidine **6** was obtained with excelent *ee* when H_2 under a palladium catalyst was used (right, Scheme 19).



Scheme 19. Derivatization of Rauhut-Currier products.

3.3.3. Mechanism proposal

A fascinating feature of the results reported herein is the functionalization of the C-3 carbon instead of the C-5 of the silyl-dienol-ether **1**, even though the latter is significantly the most nucleophilic (Figure 1). By contrast, in all the reported systems,

the functionalization of the C-5 instead of the C-3 has been observed.[23] Indeed, a natural population charge analysis of the silyl dienol ether **1a**, by means of DFT calculations, indicates a higher negative charge in C-5 than in C-3 (Figure 1). Therefore, the bifunctional catalyst should in some way direct the reactivity of substrates (**1** and **2**) towards this unprecedented reactivity. In order to understand how bifunctional organocatalyst works, numerous experimental evidence has been collected, which oriented further DFT calculations on the catalytic mechanism.

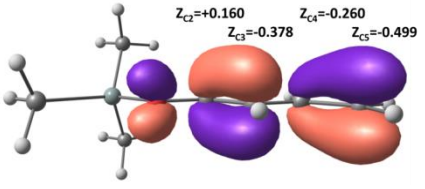


Figure 1. Highest energy ocupied molecular orbital (HOMO) found from NBO calculation in silyldienolether **1A** at the M06-2x/6-31G+(p,d) level.

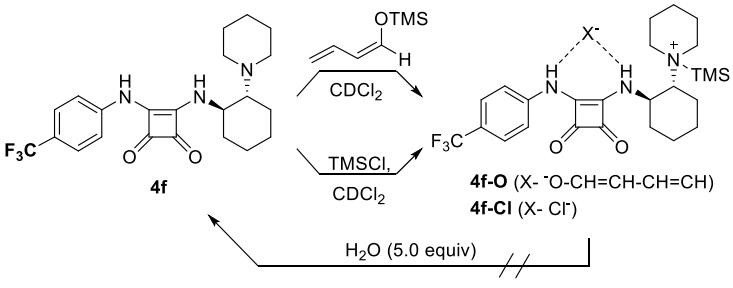
3.3.3.1. Water role

Firstly, we mixed a stoichiometric amount of the catalyst **4f** and TMSCl, obtaining a new silylated species (**4f-Cl**, Scheme 20) that contained the N+-TMS adduct and a chloride anion stabilized by hydrogen bonding (N-H・・・Cl-・・・H-N), which was confirmed by comparison of ^{1}H-NMR and ^{13}C-NMR of the initial **4f** catalyst with the **4f-Cl (Figure 2-5)**. In addition, this structure was also established by 2D-HMBC{^{1}H, ^{29}Si}, where a ^{29}Si chemical shift at 7.33 ppm, according to a Si-N bond,[24] was found. In parallel, a mixture of **4f** and silyldienol ether **1A** lead to a similar species (**4f-O, Scheme 20)**, which also contained an ammonium adduct (N+-

[23] See for example: a) S. E. Denmark, M. Xie, *J. Org. Chem*, **2007**, *72*, 7050. (b) S. E. Denmark.; G. L. Beutner, *J. Am. Chem. Soc.* **2003**, *125*, 7800. c) Y. Shimada, Y. Matsuoka, R. Irie, T. Katsuki, *Synlett*, **2004**, *57*. d) G. Bluet, G, J. M. Campagne, *J. Org. Chem*. **2001**, *66*, 4293. e) D. A. Evans, E. Hu, J. D. Burch, G. Jaeschke, *J. Am. Chem.Soc.* **2002**, *124*, 5654. f) V.Gupta, T. Sudhir, T. Mandal, C.Schneider, *Angew.Chem. Int. Ed.* **2012**, *51*, 12609.

[24] See: www.pascal-man.com/periodic-table/29Si.pdf.

TMS) and, instead of a chloride anion, contained the dienolate fragment, establishing hydrogen bonding between the two NH protons of squaramide and dienolate anion (Figures 6-8) However, the addition of 5 equiv. of water did not affect **4f-Cl** or **4f-O**, after some hours, even when solutions were heated.



Scheme 20. NMR studies in the silylation of the squaramide catalyst **4f.**

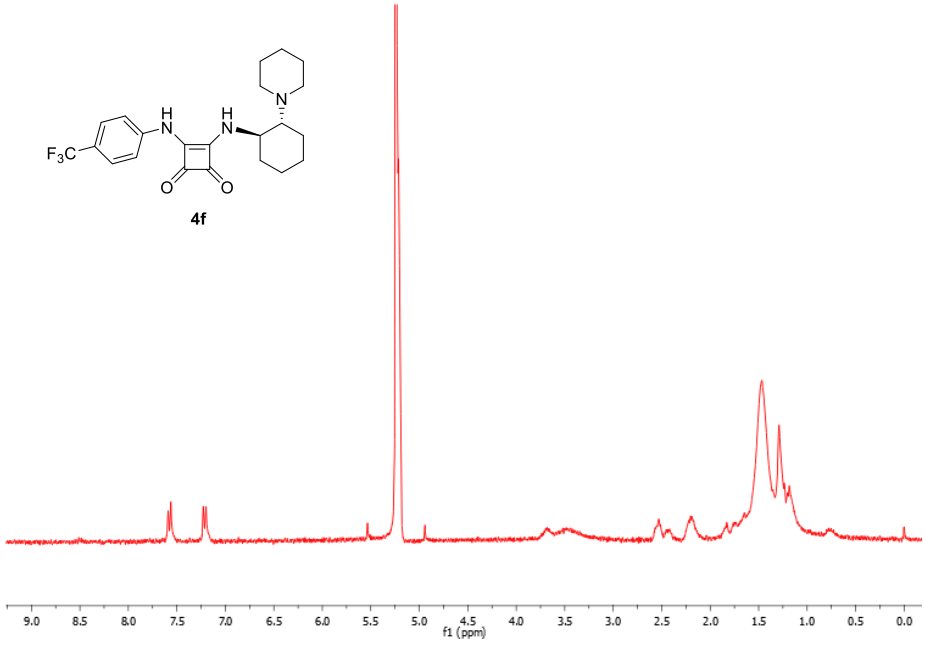


Figure 2. ^{1}H-NMR **4f** catalyst

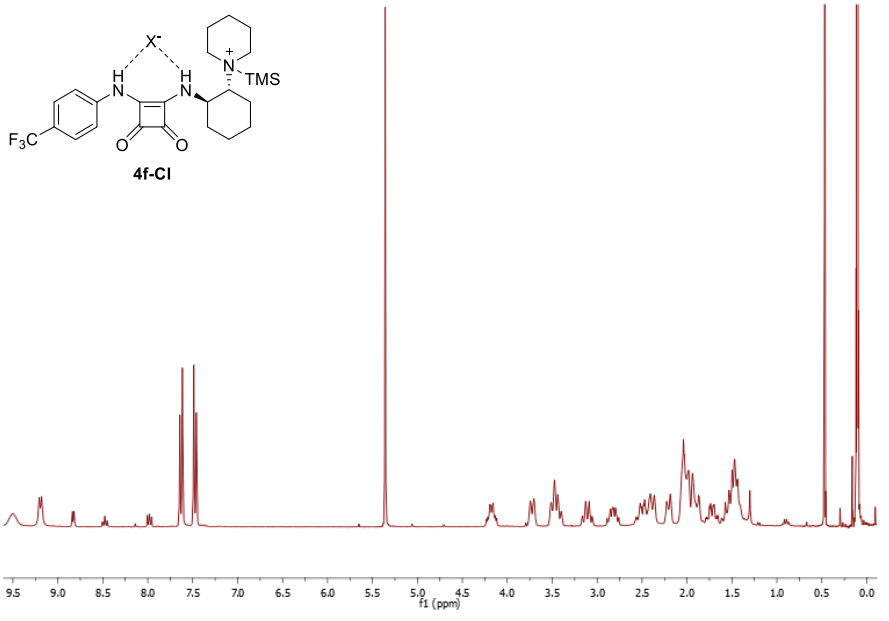


Figure 3. ^{1}H-NMR **4f-Cl**

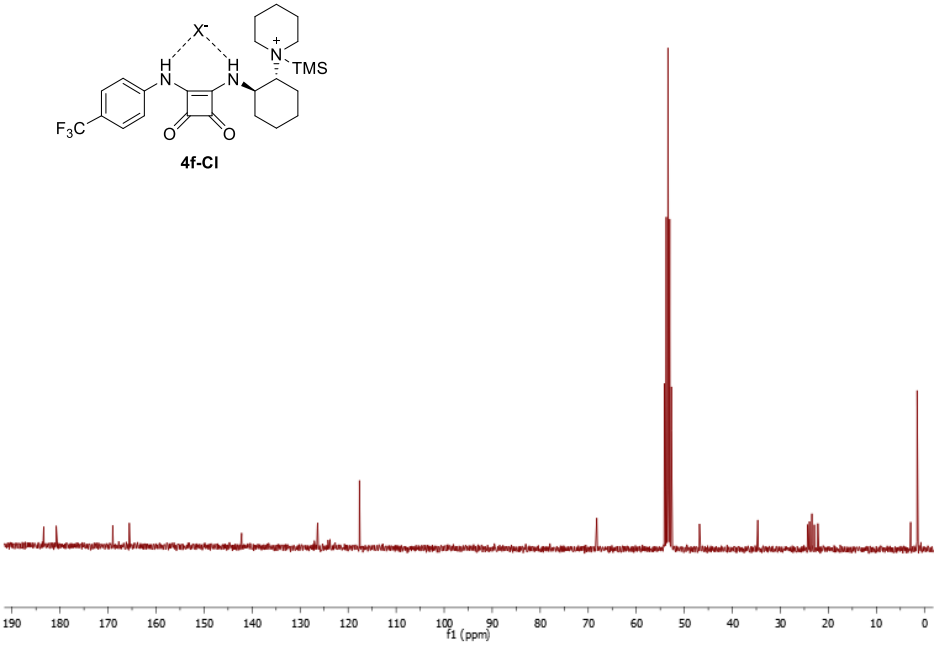


Figure 4. ^{13}C NMR of **4f-Cl**

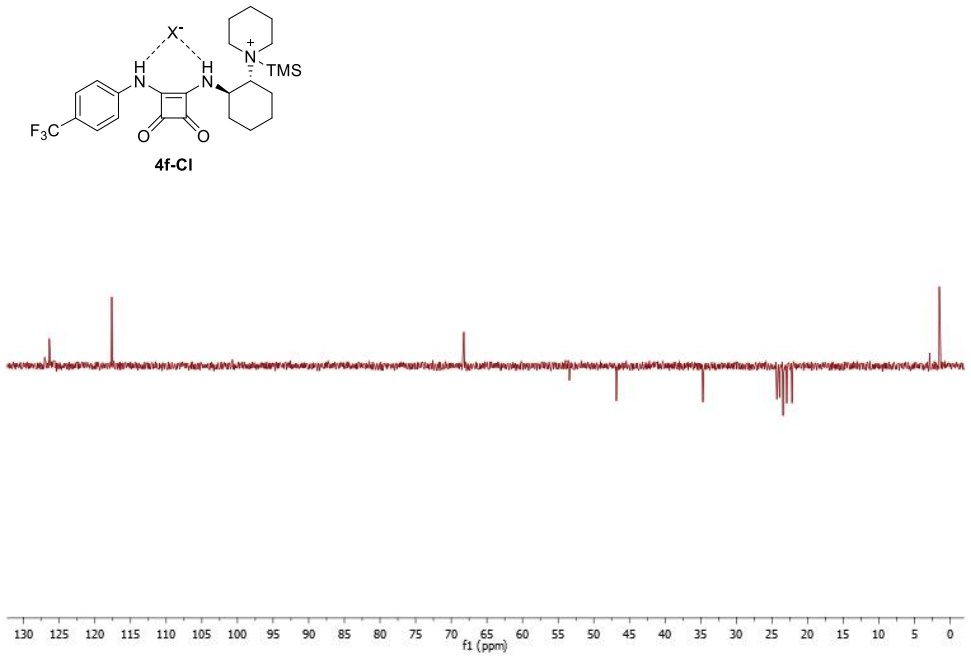


Figure 5. DEPT of **4f-Cl**

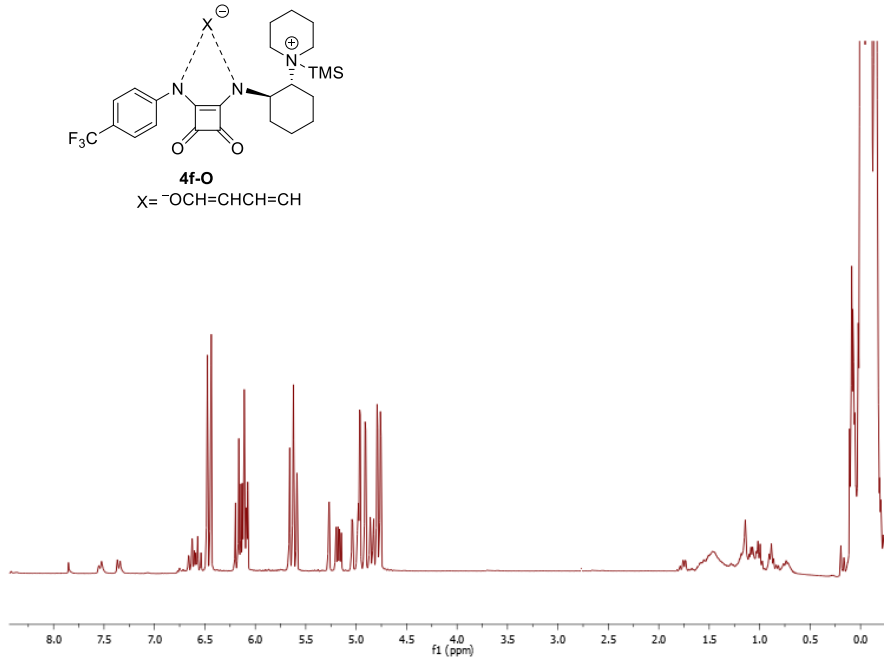


Figure 6. ^{1}H-NMR **4f-O**

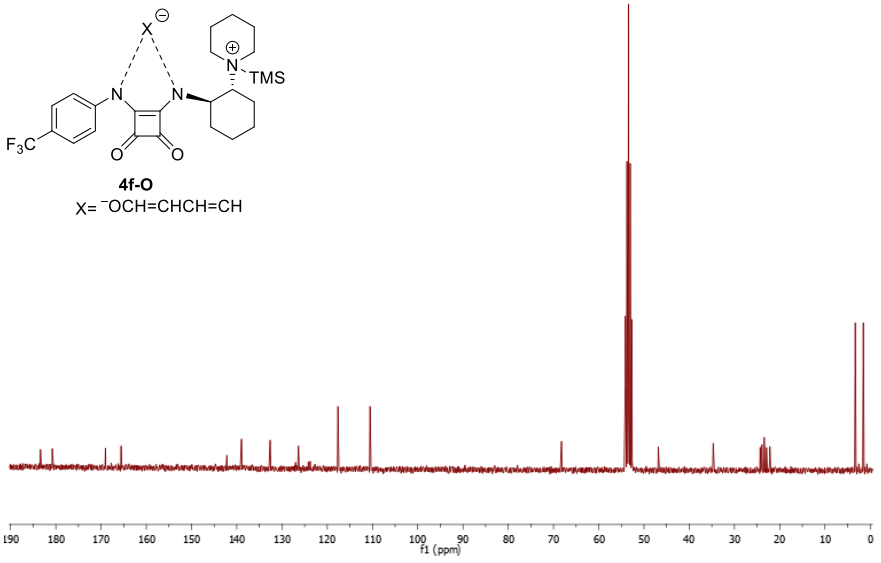


Figure 7. ^{13}C NMR of **4f-O**

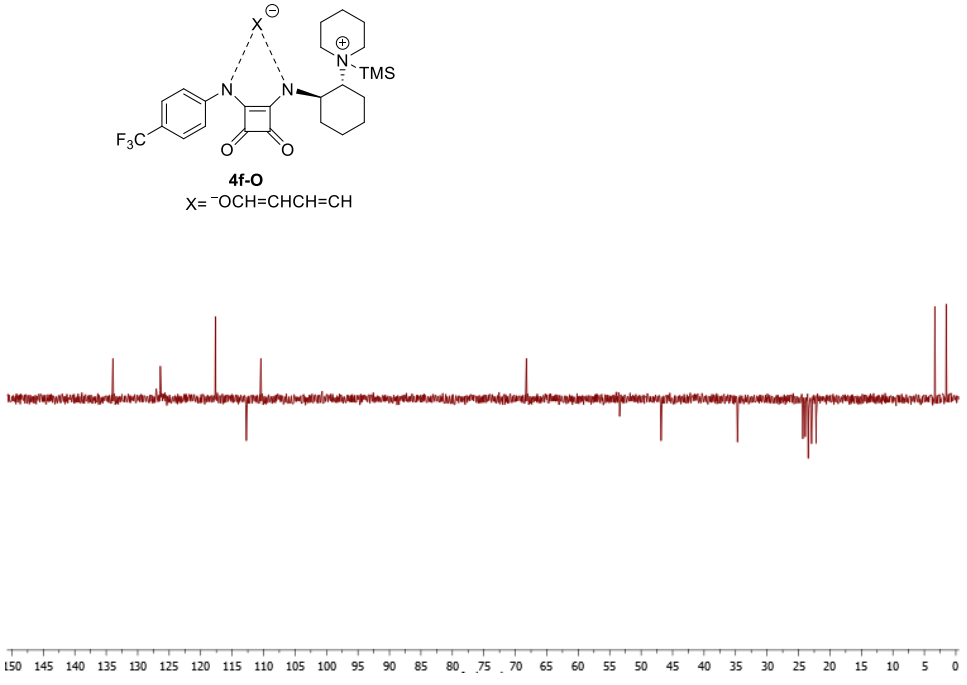


Figure 8. DEPT of **4f-O**

In addition, we carried out the NMR-titration of catalyst **4f** (Host) and silyldienolether **2a** (Guest) in the presence and absence of water (Figure 9-10). Without water, a new silylated species is formed (**4f-O**), confirmed by 2DHMBC{^{1}H, ^{29}Si}, where a new ^{29}Si chemical shift at 7.33ppm appeared. This is in accordance with a Si-N bond which is identical to the one obtained by direct silylation with TMS-Cl (**4f**-Cl). However, when water was present in the reaction media, silylation of the catalyst **4f** was not observed by 2D-HMBC{^{1}H, ^{29}Si}. Therefore, water is preventing the dead-end of the catalytic cycle and favouring the observed reactivity.

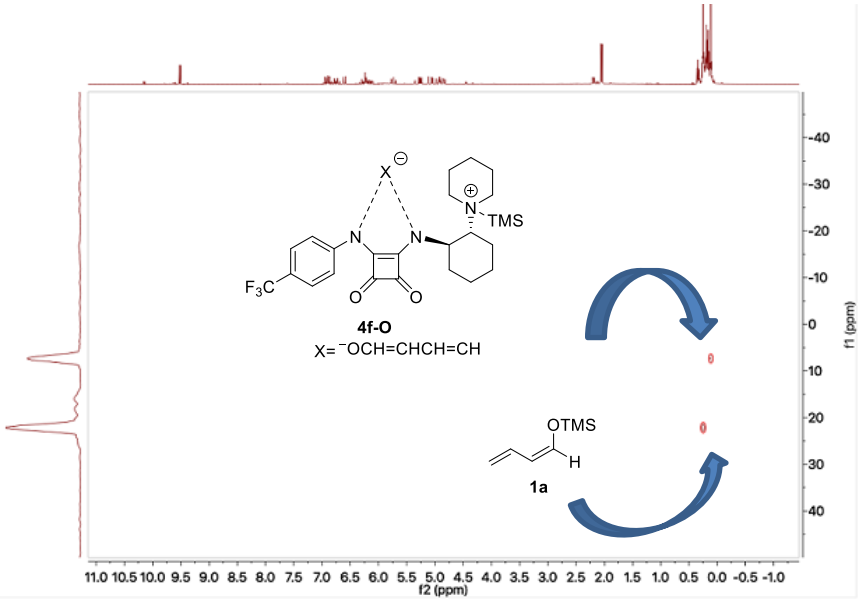


Figure 9. 2D-HMBC{^{1}H, ^{29}Si} **4f-O**

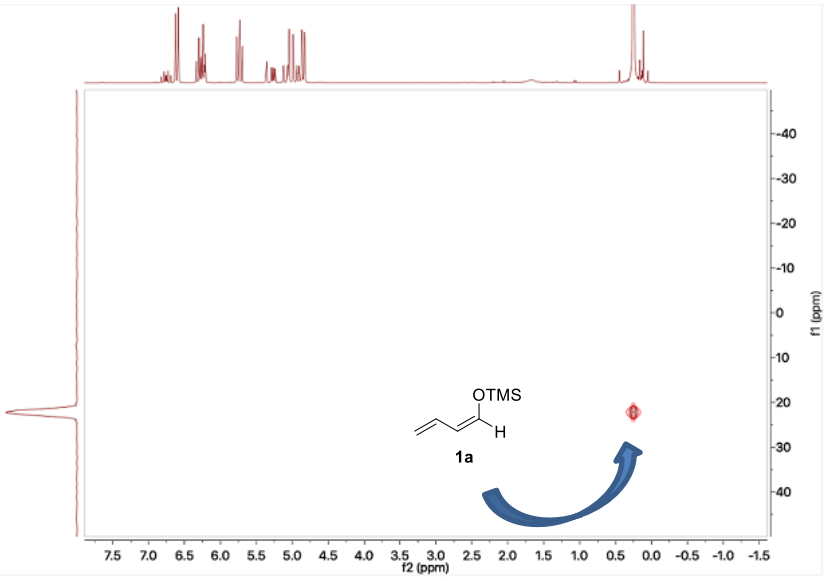


Figure 10. 2D-HMBC{^{1}H, ^{29}Si} 4f + 5 equiv. of water. Then 1 equiv. of silyl-dienol ether **1a**

Two important hints can be extrapolated from these results: Firstly, the activation of the reagent **1a** should not proceed by direct interaction with the amine of the bifunctional catalyst **4f,** because the N+-TMS adduct is unreactive to hydrolysis. Therefore, the **4f-O** species are a dead-end in the catalytic cycle. Secondly, the anion binding of the squaramide moiety[25] with the oxygen anion (N-H・・・$^{-}$O(C_4H_5)・・・H-N) indicates that the catalytic cycle can be initiated by a species in which the silyl dienol ether **1A** is coordinated to the squaramide fragment, instead of the proposal in which the nitro group is stabilized by a hydrogen bond interaction (as in the Takemotos'model[26]).

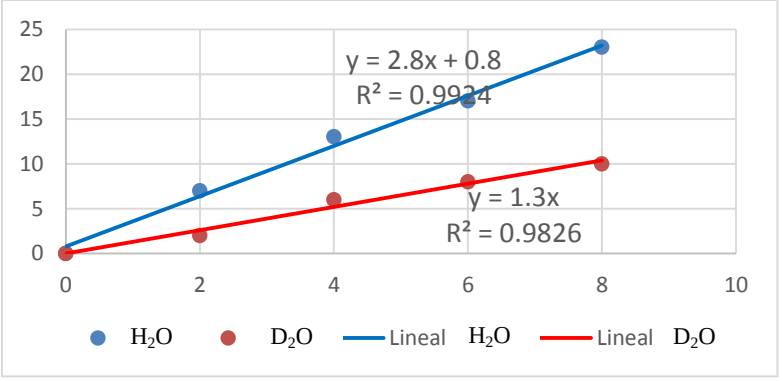
In a subsequent series of experiments, it was determined that five equivalents of water were required to obtain good yields (see supporting information). This observation suggests that the activation of reagent **1a** proceeds *via* hydrolysis. In fact, the K.I.E value of 2.2, measured by comparing the initial rates of reaction in the

[25] The coordination of oxygen anions to thiourea or squaramide has been proposed in other works. For reviews in the field, see: a) S. Beckendorf, S. Asmus, O. García Mancheño, ChemCatChem, 2012, 4, 926. b) K. Brak, E. N. Jacobsen, Angew. Chem. Int. Ed. 2013, 52, 534. c) R. Phipps, G. L. Hamilton, F. Toste, Nat. Chem. 2012, 4, 603.

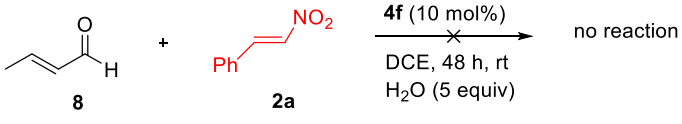
[26] T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J.Am. Chem. Soc*. **2006**, *128*, 13151.

presence of either H_2O or D_2O, indicates that the hydrolysis of silyl dienol ether is involved in the rate determining step (Figure 11).

Figure 11. Kinetic studies of the reaction.



In order to confirm that the role of the water was the hydrolysis of the silyl-dienol ether **1A** to crotonaldehyde, we carried out the reaction of **8** in the presence of catalyst **4f** in the same reaction conditions. We found no conversion at all, and therefore the process should go through the dienolate pathway as we have described (Scheme 20).



Scheme 20. No reaction was found between crotonaldehyde **8** and nitrostyrene **2a**.

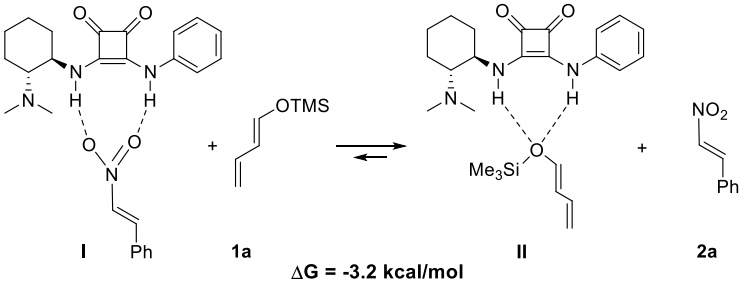
3.3.3.2. Hydrogen bond coordination

Combining all the experimental evidence presented above, we carried out a series of DFT calculations[27] in order to define a plausible pathway that could explain all the results obtained. Regarding the squaramide bifunctional catalyst we

[27] Quantum chemistry calculations were carried out using the density functional theory (DFT). In particular, geometry optimizations were performed using the M06-2X functional in combination

considered a simplified structure, in which the CF_3 group in the benzene ring was substituted by a hydrogen atom and the six-membered ring cycle NC_5H_{10} was modelled as $N(CH_3)_2$. Such simplifications decreased the computational costs by decreasing the number of basis functions and avoiding dealing with conformational equilibrium in the NC_5H_{10} ring. In order to validate this approximation, the catalytic activity of a simplified bifunctional catalyst (Ph, and NMe_2 derivative) has been experimentally tested, leading to 3a as a product with a slightly lower enantioselectivity (*ee* = 93%) and conversion (90%) than when **4f** was used.

Firstly, in order to determine the most feasible initial species, the equilibrium shown in Scheme 5 was calculated. In accordance with the experimental observations, coordination to squaramide is more favorable for the silyl dienol ether **1a** than for the nitrostyrene **2a** by 3.8 kcal/mol (**I** versus **II**). Therefore, the process studied is initiated by the hydrolysis step as a consequence of adding a water molecule to species **II** (Scheme 21).



Scheme 21. DFT studies in the equilibrium between **1a** and **2a** with the catalyst.

3.3.3.3. Energetic profile of the reaction

Dr. Rubén Más-Ballesté carried out DFT calculations in order to define a plausible pathway that could explain all the results obtained.

with the 6-31G+(d,p) basis set including dichloroethane (ε= 10.4) solvent effects with the solvation model density (SMD).

In the initial structure (see **III**, Figure 12) a hydrogen bond is found between the water molecule and the amine group (N···H = 1.81 Å).

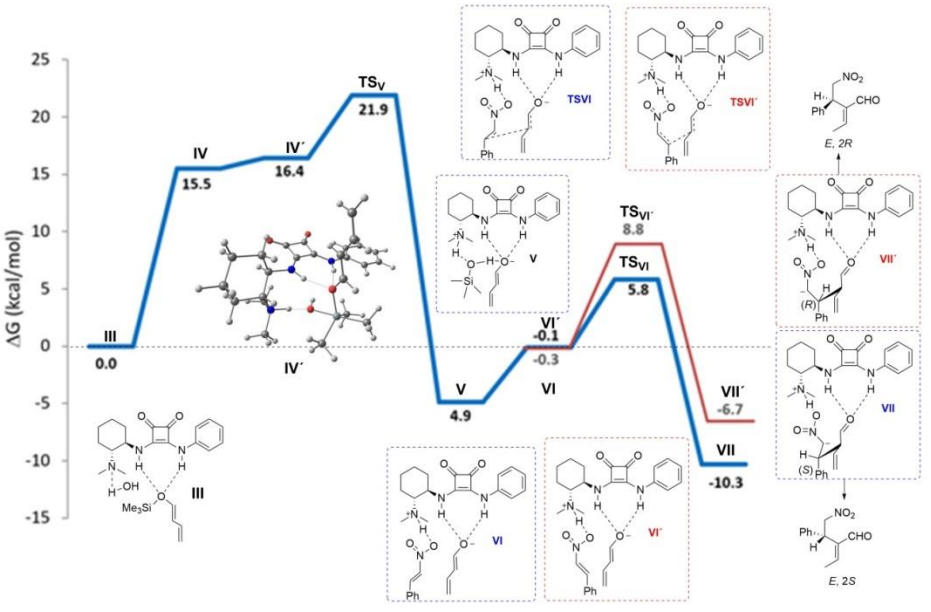


Figure 12. DFT Mo6$_{2x}$/6-$_{31}$+G(p,d) reaction energy profile in the addition of **1a** to **2a**.

In addition, the oxygen atom of the water molecule is correctly orientated to easily attack the Si center. Further evolution of this system implies at first a proton transfer from the water molecule to the amine nitrogen, followed by a nucleophilic attack of the resulting hydroxide to the silicon atom. In fact, from the starting species **III** to the **IV** there is an energetic cost of 15.5 kcal/mol. In addition, in the potential energy surface, a minimum has been located in which an hipervalent penta-coordinated RO-Si(OH)(CH_3)$_3$ silicon environment is found (structure **IV´**), and formed through the transition state **IV** (Figure 12). However, when thermal corrections are included, free energy of **IV´** is higher than **IV**. Therefore, the process from **III** to **IV´** is probably a barrierless process**.** Further evolution of such a putative intermediate **IV´** consists on an elongation of the Si-OR bond (**TS$_V$** in Figure 12) that produces the silanol byproduct and the nucleophile [$C_4H_4O^-$]. The later one is stabilized by the hydrogen bonding with the squaramide in a structure very close to the experimentally detected **4f-O** species. At this point, the hydrolysis step is finished and the C-C bond formation starts. Evolution from **V** to **VI** implies the substitution of silanol by nitrostyrene **2a**

which has an energetic cost of at least 4.7 kcal/mol, due to multiple hydrogen bonding interactions in **V**, in contrast with the simple N-H-ONO(R) interaction found in **VI**.

Moreover, this intermediate **VI** is in accordance with the well-known Papai's model.[28] Such pre-organization of the two fragments orientate the geometry of the system to specifically generate the new C-C bond (C3 with the Cβ of **2a**), even though C5 is the most nucleophilic site (see top, Figure 12). In addition to the regioselectivity, the enantioselective discrimination in the two different pathways is taking place in this step (**VI** vs **VI´**). Therefore, the C-C bond formation requires the approach of both C3 and Cβ atoms up to 2.24 and 2.29 Å, which are the distances found in the $\mathbf{TS_{VI}}$ and $\mathbf{TS_{VI}}$**'** respectively. Once adduct **VI** and **VI´** are formed, further evolution to form the key C-C bond proceeds through a lower kinetic barrier (5.9 and 9.1 Kcal/mol, respectively). As observed in the profile, one enantiomer (**VI**) follows a path with an energy barrier around 3.0 kcal/mol lower than the other one (**VI´**), accounting for the kinetic control responsible for the final enantioselectivity observed. Such energetic differences are related to the geometric constrictions imposed by the relative positions of nitrostyrene and the dienolate nucleophile both fixed by the hydrogen bonding. As a consequence, the hydrogen bonding interaction between dienolate and squaramide are different in **TSVI** and **TSVI'** (for **TSVI**: $d_{O\cdots H}$=1.76, 1.90; **TSVI´**: $d_{O\cdots H}$=1.92, 1.92, see Figure 13). The lower energy of the fixed conformation of **TSVI** as a result of the bifunctional design of the catalyst is, at the end, not only the responsible for the regio-, but also for the enantio-selectivity (compare **TSVI** and **TSVI´**). Evolution of this transition state results in species **VII** in which the C-C bond is already formed. Species **VII** and **VII´** are very close to the final product **3a** and only differs from it in a proton transfer from the amine N atom of the squaramide to the Cα of the nitronate, followed by a double bond isomerization (bottom and top-right, Figure 12).

[28] A. Hamza, G. Schubert, T. Soos, I. Papai, *J. Am. Chem. Soc*. **2006**, *128*, 13151.

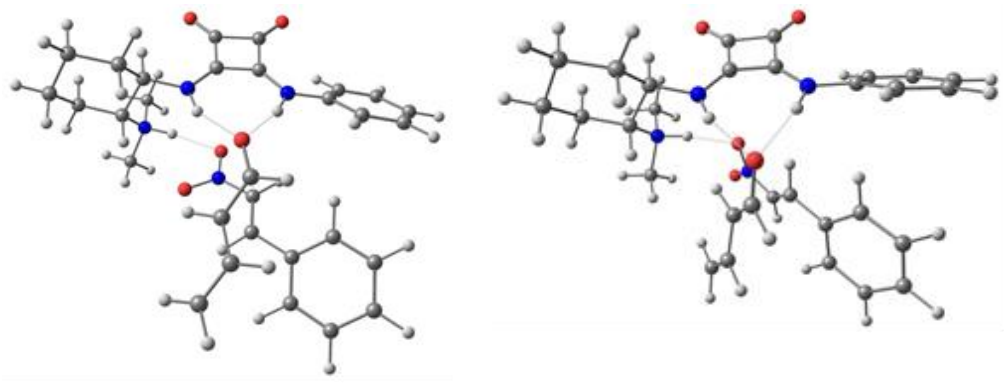


Figure 13. DFT M062x/6-31+G (p,d) of **TSVI** (left) and **TSVI'**(right).

The double bond isomerization led to the more stable product *E,* which is ~2 kcal/molmore stable than *Z* isomer (calculated by DFT, see Figure 14). Furthermore, the protonation of the nitronate **VII** would also be assisted by the generated silanol from **III** to **VI**.

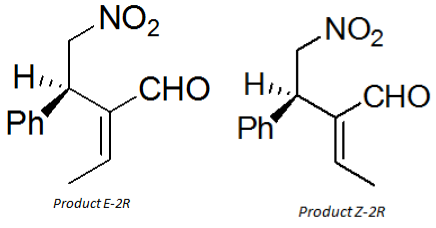


Figure 14. Comparison between both isomers of the final product.

Alternatively, the coordination of the nitroalkene to the squaramide moiety, following the Takemoto´s model,[29] was also considered (Figure 15). From intermediate **V**, the intramolecular protonation of the enolate with the ammonium fragment occurs without kinetic barrier to give the enol with simultaneous coordination of the nitroalkene to the squaramide (*pro-R* or pro-*S* face, see **VIII** and **VIII´**.). Although this pathway is also plausible, the kinetic barriers found for the C-C

[29] T. Okino, Y. Hoashi, T. Furukawa, X. N. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119.

formation in both approaches (**TS-VIII** and **TS-VIII´**) are significantly higher (12.5 and 12.3 kcal/mol) than the approaches shown in Figure 2 **TSVI** and **TSVI´**, 6.1. and 8.9 Kcal/mol).

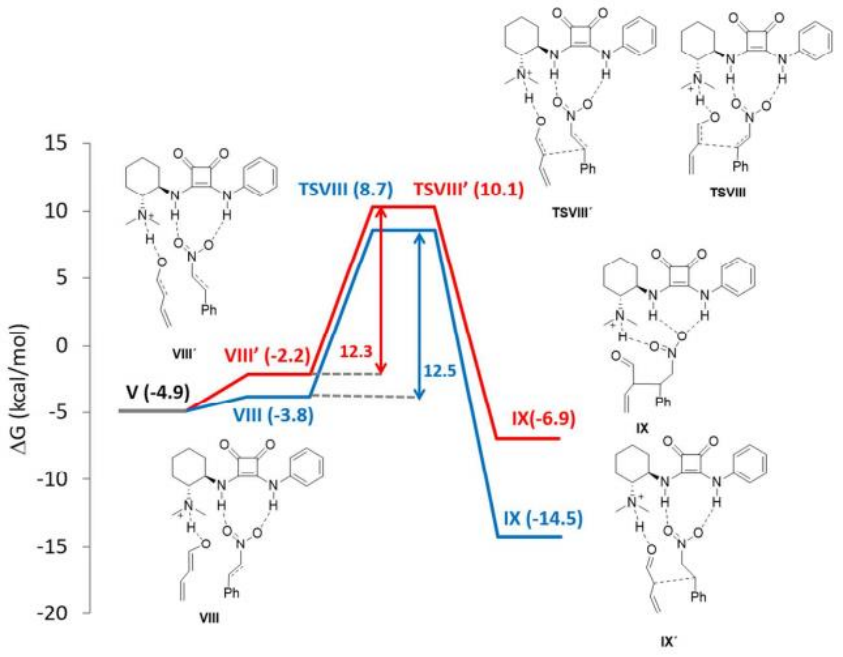


Figure 15. Energetic profile for the pathway via enolate protonation from intermediates VIII and VIII' previous to C-C bond formation for the 1,2 approximation.

To understand the energetic differences in **TSVI** and **TSVIII**, an analysis of hydrogen bond distance in the lowest energy transition states for both models has been carried out (Figure 16). A very similar interaction scheme is observed in both cases. In fact, the proton of the enol is completely transferred to the aminic nitrogen in **TSVIII** (1.058 Å, which is comparable to a similar distance in **TSVI**, 1.042 Å).

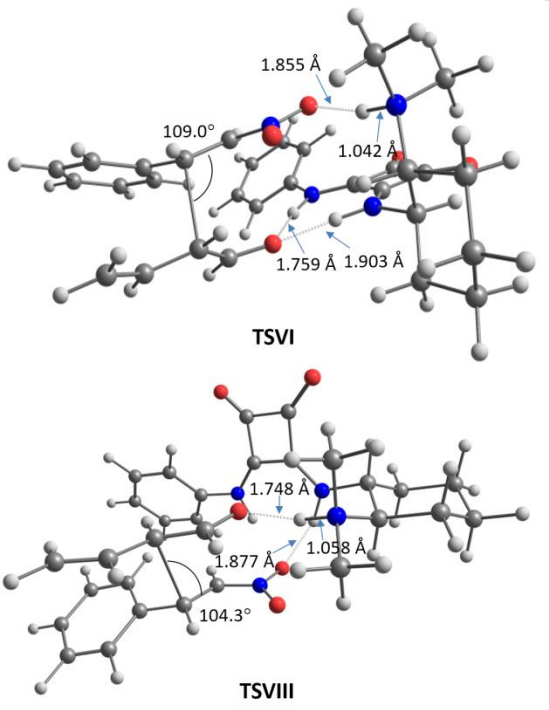


Figure 16. Detailed angles and hydrogen bond distances of TSVI (top) and TSVIII (bottom).

Consequently, an enolate stabilized by hydrogen bonding is found at both transition states (1.759 and 1.903 Å vs 1.748 Å). Therefore, a negative charge is located on the oxygen atom in **TSVIII** as in **TSVI**. The charge distribution (NPA) was in fact analyzed in both **TSVI** and **TSVIII**. Based on the collected data, the similarity between these systems from a charge distribution perspective can be verified (Figure 17). For instance, the charge of the oxygen atom in the enolate is -0.76002 for **TSVI** and -0.74707 for **TSVIII**. Moreover, the charge distribution in the newly formed C-C bonds are very similar. Therefore, the activation mode from an electronic point of view is comparable in both models.

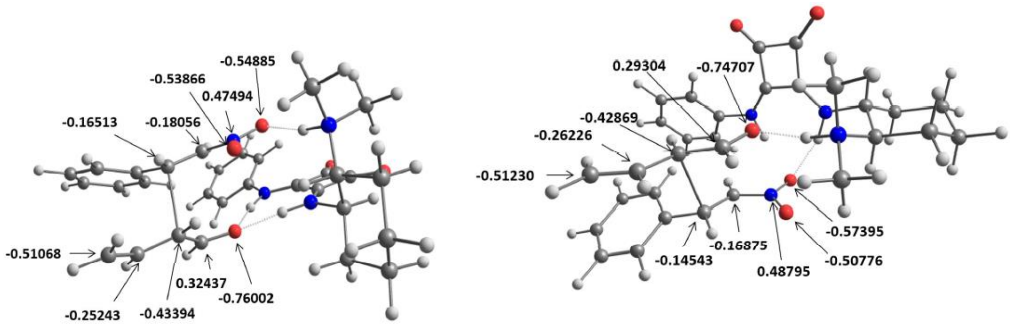
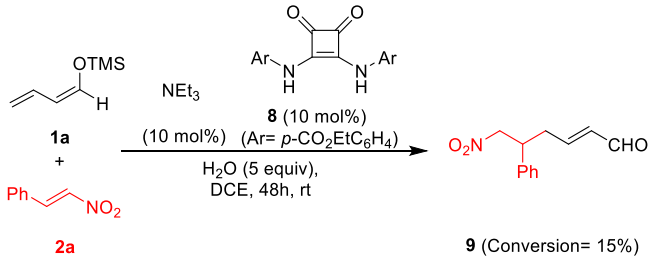


Figure 17. Charges form Natural Population Analysis (NPA) on C, O and N atoms in nucleophile and electrophile fragments in transition states corresponding to Takemoto's model (TSVIII, right) and the model presented in this work (TSVI, left).

As the electronic effects are not responsible for the system preference of one model over another, an alternative factor should be claimed. When the structure of both transition states are studied, a more tensioned structure is found for **TSVIII**. Such structural distortion can be described as the deviation of the ideal orientation angle of C-C attack. It is commonly known that the ideal Bürgi–Dunitz angle (BD angle) value is 109°, which is exactly the value found in **TSVI** (see Figure 16). However, in the case of **TSVIII** such value is 104.3°. This distortion implies a subtle energetic cost in the activation barrier in the C-C bond formation. Overall, this phenomenon is a product of the relative orientation of both substrates (nucleophile and electrophile) by hydrogen bond interactions imposed by the bifunctional design of the catalyst.

On the other hand, we were sure that the high enantio-, regio-selectivity and the high reactivity in the activation of the silyl-reagent **1** was a consequence of the bifunctional structure of catalysts **4**. Therefore, we carried out the same reaction catalyzed by triethylamine and the monofunctional squaramide **8** (Scheme 22). A very low conversion (15%) and exclusively the 1,5 addition (**9**) was observed in the crude mixture. This is in agreement with all the previous catalytic reports described in the literature which are monofunctional systems and afford only 1,5 addition products. Therefore, our new approach allows a highly enantioselective and 1,3 regioselective

functionalization of silyldienolate derivatives, giving access to Rauhut-Currier products that previously were inaccessible through other methodologies.



Scheme 22. System under two different catalysts.

3.4. Conclusions

To sum up, we have found that bifunctional catalysts are able to change the reactivity and the regioselectivity of silyl-dienol ethers. This provokes a dramatic change in the regioselectivity from the 1,5 to the 1,3 functionalization, and this fact makes possible the 1,3 addition of silyl-dienol ethers to nitroalkenes for the synthesis of tri- and tetra-substituted double bonds in the Rauhut- Currier type products.

This methodology is compatible with the use of a large variety of nitroalkenes, and different silyl-dienol ethers, to give aldehydes, esters, amides and ketones Rauhut-Currier products which are not possible to obtain by other methods.

The process takes place under smooth and non-anionic conditions with high enantiomeric excess. A rational mechanistic pathway based on DFT and mechanistic studies indicates that the hydrolysis of the silyl dienol ether is the rate determining step, followed by a C-C formation in a region- and enantioselective manner due to the appropriate orientation of the reagents in the transition state by the bifunctional catalyst.

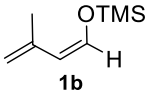
3.5. Experimental part

3.5.1. General Experimental Details

It was followed the general experimental details of section **1.9**. In addition all starting materials were purchased from commercial suppliers without further purification. Silyl-dienol ether **1a** was purchased in Sigma-Aldrich whereas **1b-1f** were synthesize according to the procedures described in the literature with light modifications.

3.5.2. Procedure for the synthesis of silyl-dienol ethers (1b-1f).

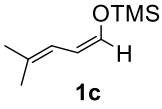
(*Z*)-Trimethyl((3-methylbuta-1,3-dien-1-yl)oxy)silane (1b)[30]



1b

To a stirred solution of 3-methylbut-2-enal (143 mmol), diethyl ether (25 ml), trimethylamine (271 mmol) and zinc chloride (1.47 mmol), was added trimethylsilyl chloride (157 mmol) at room temperature. The solution was then heated to reflux 24 h. After cooling to room temperature, *n*-pentane was added and the precipitate removed by filtration through silica. The solvent was removed in vacuo to give an oil. It was used without further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.31 (d, *J* = 11.0 Hz, 1H), 5.49 (d, *J* = 11.0 Hz, 1H), 4.75 (d, *J* = 2.0 Hz, 2H), 1.82 (s, 3H), 0.16 (m, 9H).

(*Z*)-Trimethyl((4-methylpenta-1,3-dien-1-yl)oxy)silane (1c)[31]



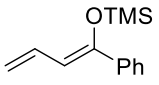
1c

A previous prepared stirred solution of lithium diisopropylamide (22.0 mmol) in tetrahydrofuran (20 mL) at 0 ºC under nitrogen was cooled to -78 ºC and (*E*)-4-methylpent-2-enal (2.30 g, 20 mmol) and trimethylsilyl chloride (4.0 mL) was added. Then the reaction mixture was warmed to room temperature (1 h). Most of tetrahydrofuran was removed by rotary evaporation to provide a white residue which was taken up in dry pentane (150 mL) and filtered through celite. The solvent was concentrated in vacuo to give an oil, which was used without further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.24 (d, *J* = 10.8 Hz, 1H),

[30] C. Schuster, *J. Org. Chem.*, **2015**, *80*, 5666.
[31] F. Kienzle, *Helv. Chim. Acta*, **1985**, *68*, 1133.

5.75 (d, *J* = 2.1 Hz, 1H), 5.10 (d, *J* = 11.1 Hz, 1H), 1.73 (s, 3H), 1.62 (s, 3H), 0.16 (s, 9H).

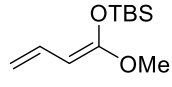
(Z)-Trimethyl((1-phenylbuta-1,3-dien-1-yl)oxy)silane (1d)[32]



1d

To a round-bottomed flask fitted with a magnetic stir bar and a septum under argon, was added (5.5 mmol, 1.1 equiv) of potassium hexamethyldisilazide and 25 ml of THF. The solution was cooled to -78 ºC and then (5.0 mmol, 1.0 equiv) of 1-phenyl-2-buten-1-one was added slowly dropwise via syringe. The resulting solution was stirred for 20 min at -72 ºC prior to the addition of (5.5 mmol, 1.1 equiv) of TMSCl via syringe. The dry ice bath was removed and the solution was allowed to warm to 0 ºC. After that, the solution was concentrated in vacuo and the residue was taken up in 50 mL of pentane. The precipitate formed was then filtered through a pad of Celite and the filtrate was concentrated in vacuo. The crude was used without further purification. **^{1}H NMR** δ 7.53 (dt, *J* = 8.4, 1.6 Hz ,2H), 7.34-7.30 (m, 2H), 7.28-7.25 (m, 1H), 6.73 (dt, *J* = 17.1, 10.5 Hz, 1H), 6.05 (d, *J* = 10.7 Hz, 1H), 5.24-5.20 (m, 1H), 5.04-5.01 (m, 1H), 0.17 (s, 9H).

(*Z*)-*tert*-Butyl((1-methoxybuta-1,3-dien-1-yl)oxy)dimethylsilane (1e)[33] To a

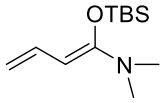


1e

stirred solution of lithium diisopropylamide (22.0 mmol) in tetrahydrofuran (20 mL) at 0 ºC, was added under nitrogen DMPU (1 ml). The solution was cooled to -78 ºC and methyl (*E*)-but-2-enoate (2.30 g, 20 mmol) and TBSCl (1.1 equiv.) was added. Then the reaction mixture was warmed to room temperature (1 h). Most of tetrahydrofuran was removed by rotary evaporation to provide a white residue which was taken up in dry pentane (150 mL) and filtered through celite. The solvent was concentrated in vacuo to give an oil, which was used without further purification. **^{1}H NMR** δ 6.53 (dt, *J* = 17.2, 10.4 Hz ,1H), 4.85 (dd, *J* = 17.1, 2.1 Hz, 1H), 4.60 (dd, *J* = 10.1, 1.9 Hz, 1H), 4.48 (d, *J* = 10.2 Hz, 1H), 3.57 (s, 3H), 0.95 (s, 9H), 0.18 (s, 6H).

[32] S. E. Denmark, *J. Org. Chem*., **2007**, *72*, 5668.
[33] J. Savard, P. Brassard, *Tetrahedron*, **1984**, *40*, 3455.

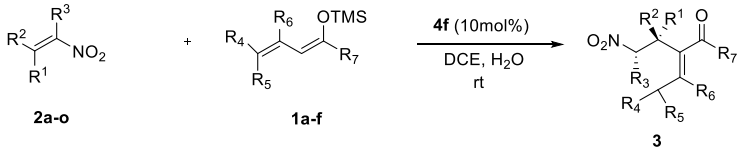
(*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-*N*,*N*-dimethylbuta-1,3-dien-1-amine (1f)[22]



1f

To a round-bottomed flask fitted with a magnetic stir bar and a septum under argon, was added (5.5 mmol, 1.1 equiv) of potassium hexamethyldisilazide and 25 ml of THF. The solution was cooled to -78 ºC and then (10.0 mmol, 1.0 equiv) of (*E*)-*N*,*N*-dimethylbut-2-enamide was added slowly dropwise via syringe. The resulting solution was stirred for 20 min at -72 ºC prior to the addition of TBSCl (11 mmol, 1.1 equiv) via syringe. The dry ice bath was removed and the solution was allowed to warm to 0 ºC. After that (18 h), the solution was concentrated in vacuo and the residue was taken up in 50 mL of pentane. The precipitate formed was then filtered through a pad of Celite and the filtrate was concentrated in vacuo. The crude was used without further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.54 (dt, *J* = 17.1, 10.5, 1H), 4.79 (dd, *J* = 17.1, 2.2, 1H), 4.61 (d, *J* = 10.7, 1H), 4.53 (dd, *J* = 10.5, 2.3, 1H), 2.58 (s, 6H), 1.00 (s, 9H), 0.16 (s, 6H).

3.5.3. General procedure for the synthesis of the Rauhut-Currier products.



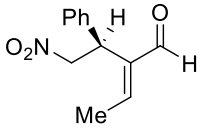
Scheme 23.

The corresponding *trans*-beta-nitrostyrene **2a-2o** (0.1 mmol, 1.0 eq.) and *N*-[(1*R*,2*R*)-2-(1-piperidinyl)cyclohexyl]-*N*′-[4-(trifluoromethyl)phenyl]squaramide **4f** (10 mol %) were dissolved in 0.3 ml of dichloroethane. Then, 3 equiv. of the corresponding silyl-dienolether **1** and 10 µl of water were added to the previous solution. The resulting mixture was stirred at room temperature. Upon completion (48-72 h determined by TLC), the solvent was removed under reduced pressure. The residue was purified by

flash column chromatography. In all cases the enantiomeric excesses were determined without any further derivatization.

Spectral Data of substrates 3a-3m:

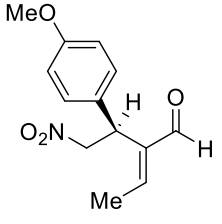
(*S*, *E*)-2-(2-Nitro-1-phenylethyl)but-2-enal (3a)



3a

Following the general procedure described above, compound **3a** was obtained in 86 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.39 (s, 1H), 7.34-7.23 (m, 5H), 6.82 (q, *J* = 9.0 Hz, 1H), 5.29 (dd, *J* = 13.1, 9.0 Hz, 1H), 5.01 (dd, *J* = 13.1, 6.5 Hz, 1H), 4.74 (t, *J* = 6.0 Hz, 1H), 2.14 (d, *J* = 9.0 Hz, 3H). **^{13}C RMN** (75 MHz, $CDCl_3$) δ 194.5, 154.8, 142.1, 137.7, 129.1, 128.0, 127.9 77.3, 41.4, 15.4. **HRMS (ESI+)**: calculated for $C_{12}H_{13}NO_3Na$ (M^++Na): 242.0799; found: 242.0787. $[\alpha]_D^{20}$= -57.2 (c = 0.83, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IB-3-1-15 column [CO_2/MeOH (99:1), 3.0 mL/min]: τ_{major} = 4.90 min, τ_{minor} = 5.71 min. (99% *ee*).

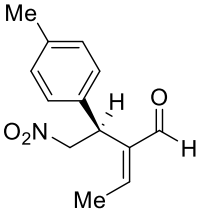
(*S*, *E*)-2-(1-(4-Methoxyphenyl)-2-nitroethyl)but-2-enal (3b)



3b

Following the general procedure described above, compound **3b** was obtained in 76 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.22 (d, *J* = 6.0 Hz, 2H), 6.84 (d, *J* = 6.0 Hz, 2H), 6.78 (q, *J* = 9.0 Hz, 1H), 5.28 (dd, *J* = 13.0, 8.9 Hz, 1H), 5.00 (dd, *J* = 13.0, 6.7 Hz, 1H), 4.67 (t, *J* =7.0 Hz, 1H), 3.77 (s, 3H), 2.13 (d, *J* = 9.0 Hz, 3H). **^{13}C RMN** (75 MHz, CDCl3) δ 195.0, 158.9, 154.6, 141.9, 129.8, 128.8, 114.1, 76.7, 55.4, 40.6, 15.2. **EM (TOF-EI+)**: calculated for $C_{13}H_{15}NO_4$: [M+] 249.0997; found: 249.1001. $[\alpha]_D^{20}$= -16.1 (c = 0.98, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IB-3-1-15 column [CO_2/MeOH (99:1), 3.0 mL/min]: τ_{major} = 6.96 min, τ_{minor} = 8.05 min. (96% *ee*).

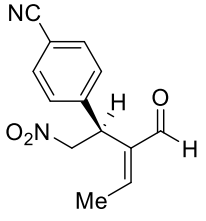
(*S*, *E*)-2-(2-Nitro-1-(p-tolyl)ethyl)but-2-enal (3c)



3c

Following the general procedure described above, compound **3c** was obtained in 77 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.25 (d, *J* = 6.0 Hz, 1H), 7.16 (m, 4H), 6.77 (q, *J* = 8.5 Hz, 1H), 5.30 (dd, *J* = 13.0, 9.0 Hz, 1H), 5.01 (dd, *J* = 13.0, 6.6 Hz, 1H), 4.69 (t, *J* = 7.0 Hz, 1H), 2.30 (s, 3H), 2.10 (d, *J* = 8.5 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl3): δ = 194.6, 154.6, 142.3, 137.6, 134.8, 129.7, 127.8, 77.3, 41.1, 21.3, 15.0. **HRMS (ESI+)**: calculated for $C_{13}H_{15}NO_3Na$ (M^++Na): 256.0946; found: 256.0944. $[\alpha]_D^{20}$= -28.4 (c = 0.44, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IB-3-1-15 column [CO_2/MeOH (99:1), 3.0 mL/min]: τ_{major} = 4.82 min, τ_{minor} = 5.71 min. (99% *ee*).

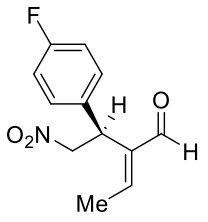
(*S*, *E*)-4-(3-Formyl-1-nitropent-3-en-2-yl)benzonitrile (3d)



3d

Following the general procedure described above, compound **3d** was obtained in 66 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.62 (d, *J* = 6.0 Hz, 2H), 7.42 (d, *J* = 6.0 Hz, 2H), 6.89 (q, *J* = 8.5 Hz, 1H), 5.16 (m, 2H), 4.79 (t, *J* = 7.0 Hz, 1H), 2.15 (d, *J* = 8.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 194.5, 155.3, 143.0, 141.0, 133.0, 128.7, 118.4, 111.9, 75.9, 41.4, 15.4. **HRMS (ESI+)**: calculated for $C_{13}H_{12}N_2O_3Na$ (M^++Na): 267.0750; found: 267.0740. $[\alpha]_D^{20}$= -31.95 (c = 0.81, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IB-3-1-30 column [CO_2/MeOH (99:1), 3.0 mL/min]: τ_{major} =16.10 min, τ_{minor} = 17.11 min. (>99.9% *ee*).

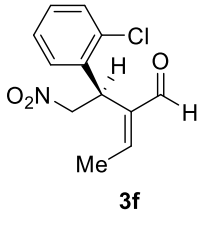
(*S*, *E*)-2-(1-(4-Fluorophenyl)-2-nitroethyl)but-2-enal (3e)



3e

Following the general procedure described above, compound **3e** was obtained in 81 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.28 (dd, *J* = 9.0, 4.9 Hz, 2H), 7.00 (dd, *J* = 9.0, 3.0 Hz, 2H), 6.80 (q, *J* = 9.0Hz, 1H), 5.24 (dd, *J* = 13.1, 8.7 Hz, 1H), 5.03 (dd, *J* = 13.1, 6.8 Hz, 1H), 4.71 (t, *J* = 7.0 Hz, 1H), 2.14 (d, *J* = 9.0 Hz, 3H).**^{13}C RMN** (75 MHz, CDCl3) δ 194.5, 161.1 (d, J_{CF} = 247.0 Hz), 154.9, 141.7, 133.5, 129.5 (d, J_{CF} = 7.5 Hz), 116.1 (d, J_{CF} =21.7 Hz), 77.3, 40.5, 15.5. **HRMS (ESI+)**: calculated for $C_{12}H_{12}NO_3FNa$ (M^++Na): 260.0700; found: 260.0693. $[\alpha]_D^{20}$= -28.42 (c = 0.82, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IB-3-1-15 column [CO_2/MeOH (99:1), 3.0 mL/min]: τ_{major} =4.26 min, τ_{minor} = 4.47 min (>99.9% *ee*).

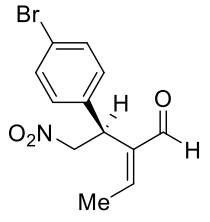
(*S*, *E*)-2-(1-(2-Chlorophenyl)-2-nitroethyl)but-2-enal (3f)



3f

Following the general procedure described above, compound **3f** was obtained in 81% yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.49 (dd, J = 7.1, 2.4 Hz, 1H), 7.41 (dd, *J* = 6.2, 3.1 Hz, 1H), 7.32 – 7.22 (m, 2H), 6.88 (q, *J* = 7.1 Hz, 1H), 5.40 (dd, *J* = 13.0, 9.8 Hz, 1H), 5.20 (dd, *J* = 9.7, 5.6 Hz, 1H), 4.90 (dd, *J* = 13.0, 5.6 Hz, 1H), 2.16 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 195.2, 156.5, 139.9, 134.7, 133.32, 130.1(2), 129.2, 127.5, 75.3, 38.1, 16.0. **HRMS (ESI+):** calculated for $C_{12}H_{12}NO_3ClNa$ (M^++Na): 276.0392; found: 276.0397. $[\alpha]_D^{20}$= -23.58 (c = 1.06, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IB-3-1-15 column [CO_2/MeOH (99:1), 3.0 mL/min]: τ_{major} =5.01 min, τ_{minor} = 5.70 min (98% *ee*).

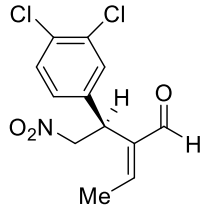
(*S*, *E*)-2-(1-(4-Bromophenyl)-2-nitroethyl)but-2-enal (3g)



3g

Following the general procedure described above, compound **3g** was obtained in 83% yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.82 (q, *J* = 7.1 Hz, 1H), 5.23 (dd, *J* = 13.2, 8.6 Hz, 1H), 5.04 (dd, *J* = 13.2, 6.8 Hz, 1H), 4.69 (t, *J* = 7.6 Hz, 1H), 2.13 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 194.5, 155.1, 141.7, 136.7, 132.4, 129.6, 122.0, 76.6, 40.7, 15.4. HRMS (ESI+): calculated for $C_{12}H_{12}NO_3BrNa$ (M^++Na): 319.9891; found: 319.9892. $[\alpha]_D^{20}$= -37.40 (c = 0.54, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IB-3-1-15 column [CO_2/MeOH (99:1), 3.0 mL/min]: τ_{major} = 9.88 min, τ_{minor} = 11.91 min (>99.9% *ee*).

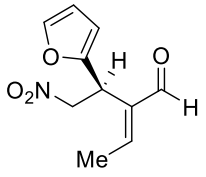
(*S*, *E*)-2-(1-(3,4-Dichlorophenyl)-2-nitroethyl)but-2-enal (3h)



3h

Following the general procedure described above, compound **3h** was obtained in 79 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.38 (s, 1H), 7.15 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.85 (q, *J* = 7.1 Hz, 1H), 5.19 (dd, *J* = 13.2, 8.5 Hz, 1H), 5.05 (dd, *J* = 13.3, 6.9 Hz, 1H), 4.69 (t, *J* = 7.6 Hz, 1H), 2.14 (d, *J* = 7.1 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 194.5, 155.1, 140.7, 137.7, 133.7, 132.1, 131.0, 130.3, 127.3, 76.2, 40.4, 15.4. **HRMS (ESI+):** calculated for $C_{12}H_{11}NO_3Cl_2Na$ (M^++Na): 310.0013; found: 310.0008. $[\alpha]_D^{20}$= -26.58 (c = 0.63, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IB-3-1-15 column [CO_2/MeOH (99:1), 3.0 mL/min]: τ_{major} =10.33 min, τ_{minor} = 12.62 min (97% *ee*).

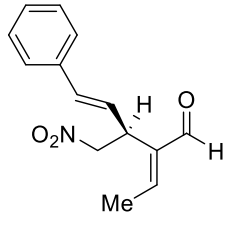
(*S*, *E*)-2-(1-(Furan-2-yl)-2-nitroethyl)but-2-enal (3i)



3i

Following the general procedure described above, compound **3i** was obtained in 74 % yield as a yellow oil after 48 h of reaction (92:8 diasteromeric ratio). The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, CDCl3) δ 9.39 (s, 1H), 7.31 (d, *J* = 1.4 Hz, 1H), 6.88 (q, *J* = 7.1 Hz, 1H), 6.30 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.11 (d, *J* = 3.3 Hz, 1H), 5.06 (dd, *J* = 7.5, 2.6 Hz, 2H), 4.91 (m, 1H), 2.11 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl3): δ 193.6, 155.1, 150.3, 142.0, 139.2, 111.1, 107.2, 74.9, 34.7, 15.4. **HRMS (ESI+):** calculated for $C_{10}H_{11}NO_4Na$ (M^++Na): 232.0574; found: 232.0580. $[\alpha]_D^{20}$= -55.2 (c = 1.25, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IA-0.5-1-60 column [CO_2/MeOH (99:1), 0.5 mL/min]: τ_{minor} =37.45 min, τ_{major} = 45.90 min (93% *ee*).

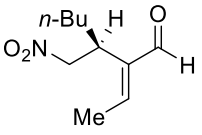
(*S*, 2*E*, 4*E*)-2-Ethylidene-3-(nitromethyl)-5-phenylpent-4-enal (3j)



3j

Following the general procedure described above, compound **3j** was obtained in 85 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.39 (s, 1H), 7.37 – 7.20 (m, 5H), 6.80 (q, *J* = 7.1 Hz, 1H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.34 (dd, *J* = 15.8, 8.3 Hz, 1H), 4.91 (dd, *J* = 12.4, 8.7 Hz, 1H), 4.76 (dd, *J* = 10.9, 5.2 Hz, 1H), 4.30 (q, *J* = 7.7 Hz, 1H), 2.12 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 194.5, 154.1, 141.4, 136.0, 133.7, 128.7, 128.4, 126.7, 124.3, 76.8, 40.1, 15.1. **HRMS (ESI+):** calculated for $C_{14}H_{15}NO_3Na$ (M++Na): 268.0951; found: 268.0944. $[\alpha]_D^{20}$= -51.9 (c = 1.10, CHCl3). The enantiomeric excess was determined by SFC using Chiralpak-IB-3-1-15 column [CO_2/MeOH (99:1), 3.0 mL/min]: τ_{minor} =9.41 min, τ_{major} = 10.00 min. (94% *ee*).

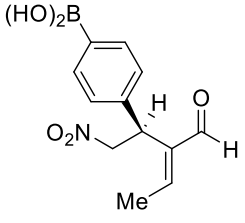
(*S*, *E*)-2-Ethylidene-3-(nitromethyl)heptanal (3k)



3k

Following the general procedure described above, compound **3k** was obtained in 82 % yield as a yellow oil after 48 h of reaction (81:19 diasteromeric ratio). The crude product was purified by flash column chromatography using 6:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.34 (s, 1H), 6.79 (q, *J* = 7.1 Hz, 1H), 4.84 (dd, *J* = 12.3, 9.6 Hz, 1H), 4.54 (dd, *J* = 12.4, 5.5 Hz, 1H), 3.49 – 3.36 (m, 1H), 2.02 (d, *J* = 7.1 Hz, 3H), 1.63 – 1.49 (m, 2H), 1.36 – 1.12 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 194.8, 155.4, 147.7, 141.4, 78.9, 36.4, 29.7, 22.4, 15.4, 13.7. **HRMS (ESI+):** calculated for $C_{10}H_{17}NO_3Na$ (M^++Na): 222.1094; found: 222.1087. $[\alpha]_D^{20}$= -20.8 (c = 0.90, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IA-0.5-1-60 column [CO_2/MeOH (99:1), 0.5 mL/min]: τ_{major} =18.74 min, τ_{minor} = 21.91 min (81% *ee*).

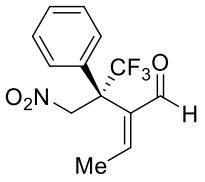
(*S*, *E*)-(4-(3-Formyl-1-nitropent-3-en-2-yl)phenyl)boronic acid (3l)



3l

Following the general procedure described above, compound **3l** was obtained in 71 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 1:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 6.77-6.58 (m, *J* = 7.8, 4.1 Hz, 3H), 5.27 (dd, *J* = 13.0, 8.9 Hz, 1H), 5.00 (dd, *J* = 13.0, 6.7 Hz, 1H), 4.71 – 4.62 (m, 1H), 2.12 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 194.7, 155.2, 154.5, 141.9, 129.9, 129.2, 115.8, 77.6, 41.0, 15.5. **HRMS (EI+):** calculated for $C_{12}H_{15}NO_5B$ (M^++H+): 264.1094; found: 264.1087. $[\alpha]_D^{20}$= -24.3 (c = 0.74, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IB-3-5-30 column [CO_2/MeOH (95:5), 3.0 mL/min]: τ_{minor} =9.79 min, τ_{major} = 10.17 min. (>99.9% *ee*).

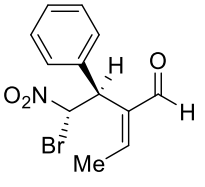
(*R*, *E*)-2-(1,1,1-Trifluoro-3-nitro-2-phenylpropan-2-yl)but-2-enal (3m)



3m

Following the general procedure described above, compound **3m** was obtained in 73 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.39 (s, 1H), 7.46-7.27 (m, 5H), 6.77 (q, *J* = 9.0 Hz, 1H), 5.61 (d, *J* = 13.1 Hz, 1H), 5.45 (d, *J* = 13.1 Hz, 1H), 2.14 (d, *J* = 9.0 Hz, 3H**).** **^{13}C NMR** (75 MHz, $CDCl_3$): δ 194.5, 154.6, 141.6, 137.5, 133.2, 128.9, 127.7, 127.6, 121.3 (q, J_{CF}= 262 Hz), 76.4, 15.1. **HRMS (ESI+):** calculated for $C_{13}H_{12}NO_3F_3Na$ (M^++Na): 310.0697; found: 310.0691. $[\alpha]_D^{20}$= + 32.3 (c = 0.86, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak- IB-3-15-20 column [CO_2/MeOH (85:15), 3.0 mL/min]: τ_{minor} = 13.10 min, τ_{major} = 14.32 min. (96% *ee*).

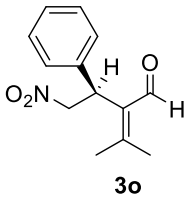
(*E*)-2-((1*S*,2*S*)-2-Bromo-2-nitro-1-phenylethyl)but-2-enal (3n)



3n

Following the general procedure described above, compound **3n** was obtained in 75 % yield as a white solid after 48 h of reaction (91:9 diasteromeric ratio). The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.43 – 7.33 (m, 5H), 7.25 (d, *J* = 11.1 Hz, 1H), 6.77 (q, *J* = 7.1 Hz, 1H), 4.72 (d, *J* = 11.1 Hz, 1H), 2.19 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 194.5, 155.8, 141.0, 136.1, 129.3, 129.0, 128.4, 79.9, 50.4, 15.1. **HRMS (ESI+):** calculated for $C_{12}H_{12}NO_3BrNa$ (M^++Na): 319.9887; found: 319.9892. $[\alpha]_D^{20}$= -22.4 (c = 0.81, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IB-0.5-0.5-35 column [CO_2/MeOH (99.5:0.5), 0.5 mL/min]: τ_{major} = 21.19 min, τ_{minor} = 23.59 min. (92% *ee*).

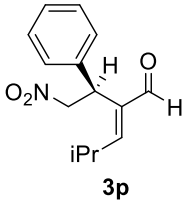
(*S*)-3-Methyl-2-(2-nitro-1-phenylethyl)but-2-enal (3o)



3o

Following the general procedure described above, compound **3o** was obtained in 81 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.14 (d, *J* = 1.4 Hz, 1H), 7.34 – 7.22 (m, 5H), 5.26 (dd, *J* = 12.8, 8.7 Hz, 1H), 5.05 (dd, *J* = 12.8, 6.5 Hz, 1H), 4.79 (t, *J* = 7.5 Hz, 1H), 2.26 (s, 3H), 2.15 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) 191.2, 160.2, 139.1, 134.7, 128.9, 127.8, 127.4, 77.3, 42.5, 23.7, 21.1. **HRMS (ESI+):** calculated for $C_{13}H_{15}NO_3Na$ (M^++Na): 256.0933; found: 256.0944. $[\alpha]_D^{20}$ = -52.4 (c = 1.0, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IB-1-5-20 column [CO_2/MeOH (95:5), 1 mL/min]: τ_{major} = 9.17 min, τ_{minor} = 9.59 min (95% *ee*).

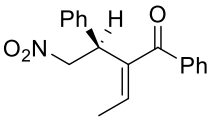
(*S, E*)-4-Methyl-2-(2-nitro-1-phenylethyl)pent-2-enal (3p)



3p

Following the general procedure described above, compound **3p** was obtained in 69 % yield as a yellow oil after 48 h of reaction. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.35-7.24 (m, 5H), 6.33 (d, *J* = 6.2 Hz, 1H), 5.34 (t, *J* = 8.0 Hz, 1H), 5.22 (dd, *J* = 12.4, 8.0 Hz, 1H), 4.97 (dd, *J* = 12.4, 8.0 Hz, 1H), 3.01 (m, 1H), 1.77 (d, *J* = 6.8 Hz, 3H), 1.72 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 194.6, 154.4, 141.8, 137.4, 134.5, 128.6, 127.5, 77.2, 40.8, 31.2, 20.9, 15.1. **HRMS (ESI+):** calculated for $C_{14}H_{17}NO_3Na$ (M^++Na): 270.1097; found: 270.1090. $[\alpha]_D^{20}$ = -33.1 (c = 0.9, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IB-1-5-20 column [CO_2/MeOH (95:5), 1 mL/min]: τ_{minor} =17.23 min, τ_{major} = 18.73 min. (93% *ee*).

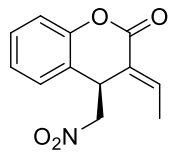
(*S, E*)-2-(2-Nitro-1-phenylethyl)-1-phenylbut-2-en-1-one (3q)



3q

Following the general procedure described above, compound **3q** was obtained in 75 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.71 – 7.19 (m, 10H), 6.40 (q, *J* = 7.0 Hz, 1H), 5.28 (dd, *J* = 12.9, 8.7 Hz, 1H), 5.04 (dd, *J* = 13.0, 6.6 Hz, 1H), 4.15 (t, *J* = 5.4 Hz, 1H), 1.91 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 198.2, 143.7, 139.4, 138.5, 138.0, 132.0, 129.5, 128.9, 128.1, 127.8, 127.5, 76.8, 43.0, 13.4. **HRMS (ESI+):** calculated for $C_{18}H_{17}NO_3Na$ (M^++Na): 318.0933; found: 318.0944. $[\alpha]_D^{20}$ = -29.4 (c = 0.82, $CHCl_3$). The enantiomeric excess was determined by using Chiralpak-IB-3-5-20 column [CO_2/MeOH (95:5), 3 mL/min]: τ_{minor}=3.86 min, τ_{major} = 4.26 min. (95% *ee*).

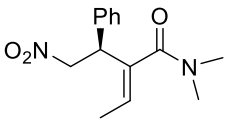
(*S, E*)-3-Ethylidene-4-(nitromethyl)chroman-2-one (3r)



3r

Following the general procedure described above, compound **3r** was obtained in 68 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 4.5 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.27 – 7.21 (m, 2H), 6.81 (q, *J* = 6.4 Hz, 1H), 5.42 (dd, *J* = 13.6, 10.1 Hz, 1H), 5.23 (dd, *J* = 13.6, 10.1 Hz, 1H), 4.62 (dd, *J* = 13.6, 10.1 Hz, 1H), 2.22 (d, *J* = 3.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 166.7, 156.4, 139.3, 135.2, 134.6, 129.5, 128.2, 126.4, 126.2, 75.1, 38.3, 15.4. **HRMS (ESI+):** calculated for $C_{12}H_{11}NO_4Na$ (M^++Na): 257.0433; found: 257.0487. $[\alpha]_D^{20}$ = -56.4 (c = 0.6, $CHCl_3$). The enantiomeric excess was determined by SFC previous reduction of the obtained aldehyde usingChiralpak-IA-3-20-20 column [CO_2/MeOH (80:20), 3.0 mL/min]: τ_{minor}= 7.66 min,τ_{major}= 6.47 min. (93% *ee*).

(*S*, *E*)-*N*, *N*-Dimethyl-2-(2-nitro-1-phenylethyl)but-2-enamide (3s)

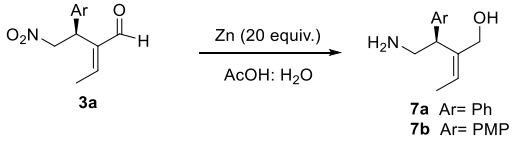


3s

Following the general procedure described above, compound **3s** was obtained in 77 % yield as a yellow oil after 72 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 – 7.07 (m, 5H), 6.53 (q, *J* = 7.1 Hz, 1H), 5.28 (dd, *J* = 12.9, 8.7 Hz, 1H), 5.04 (dd, *J* = 13.0, 6.6 Hz, 1H), 4.79 (t, *J* = 7.5 Hz, 1H), 2.51 (s, 6H), 1.89 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 171.1, 152.4, 138.5, 133.2, 128.1, 126.3, 113.1, 77.7, 53.6, 32.3, 12.4. **HRMS (ESI+):** calculated for $C_{14}H_{18}N_2O_3Na$ (M^++Na): 285.0977; found: 285.0971. $[\alpha]_D^{20}$ = -42.4 (c = 0.80, $CHCl_3$). The enantiomeric excess was determined by using Chiralpak-IA-3-20-20 column [CO2/MeOH (95:5), 3 mL/min]: τ_{minor} = 8.28 min, τ_{major} = 6.44 min. (95% *ee*).

3.5.4. DERIVATIZATIONS:

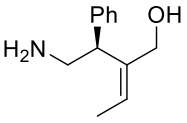
3.5.4.1. General Procedure for the reduction of the NO_2 and aldehyde groups.



Scheme 24.

1 equiv. (0.1 mmol) of **3a** dissolved in a mixture of AcOH: H_2O (1:1), was added 20 equiv. (2 mmol) of dust Zn. After 45 min of reaction (followed by TLC), the solution was filtered through Celite and a solution of NaOH 4M was added until neutral pH. The solution is then change to a separatory funnel with 5 ml of dichloromethane. The aqueous phase was extracted (5 x 5 mL dichloromethane) and the combined organic phases were washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated to afford the product quantitatively, which was used without further purification.

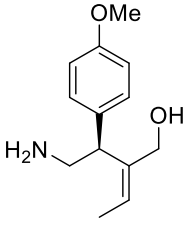
(*S*, *E*)-2-(2-Amino-1-phenylethyl)but-2-en-1-ol (7a)



7a

Following the general procedure described above, compound **7a** was obtained in 77 % yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 – 7.21 (m, 5H), 5.59 (q, *J* = 6.4 Hz, 1H), 5.1 (s, 1H), 4.02 (t, *J* = 5.4 Hz, 1H), 3.76 (dd, *J* = 6.7, 3.8 Hz, 2H), 3.52 (dd, *J* = 13.6, 6.2 Hz, 1H), 2.98 (dd, *J* = 13.6, 6.2 Hz, 1H), 1.51 (d, *J* = 3.3 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$): 135.4, 134.0, 130.2, 128.6, 126.3, 124.5, 62.3, 46.1, 37.4, 15.2. **HRMS (ESI+)**: calculated for $C_{12}H_{17}NONa$ (M^++Na): 214.1197; found: 214.1187. The enantiomeric excess was determined by HPLC using Chiralpak-IA-1-5-40 column [Hexane/Isopropanol (95:5), 1 mL/min]: τ_{minor} =26.03 min, τ_{major} = 26.90 min. (98% *ee*).

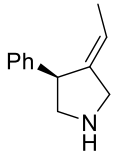
(*S*, *E*)-2-(2-Amino-1-(4-methoxyphenyl)ethyl)but-2-en-1-ol (7b)



7b

Following the general procedure described above, compound **7b** was obtained in 84 % yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.23 (d, J = 6.0 Hz, 2H), 6.75 (d, *J* = 6.0 Hz, 2H), 5.25 (q, *J* = 6.4 Hz, 1H), 5.25 (s, 1H), 3.62 (s, 3H), 3.62 (t, *J* = 5.4 Hz, 1H) 3.54 (dd, *J* = 6.7, 3.8 Hz, 2H), 3.48 (dd, *J* = 13.6, 6.1 Hz, 1H), 2.83 (dd, *J* = 13.6, 10.1 Hz, 1H), 1.53 (d, *J* = 3.3 Hz, 3H).**^{13}C NMR** (75 MHz, CDCl3): 158.5, 154.3, 141.2, 129.0, 128.4, 114.5, 65.8, 54.6, 48.1, 39.4, 14.1. **HRMS (ESI+):** calculated for $C_{13}H_{19}NO_2Na$ (M^++Na): 244.1297; found: 244.1285. The enantiomeric excess was determined by HPLC using Chiralpak-IA-3-5-20 column [Hexane/Isopropanol (95:5), 3 mL/min]: τ_{major} = 6.91 min, τ_{minor} = 8.37 min. (95% *ee*).

(*S*, *E*)-3-Ethylidene-4-phenylpyrrolidine (6a)



6a

The corresponding **3a** (1 equiv., 0.1 mmol) was dissolved in anhydrous methanol (2 ml). 10% of Pd\C was added and the solution was stirred under H_2 for 4 hours. Once completed, the crude was purified via column chromatography (Hexane/ AcOEt 3:1 to 1:1) to afford the desire product as a yellow oil (67% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 – 7.21 (m, 5H), 5.61 (q, *J* = 6.4 Hz, 1H), 3.67 (d, *J* = 13.1 Hz, 1H), 3.55 (t, *J* = 6.4, 1H), 3.50

(dd, *J* = 12.3, 6.2 Hz, 1H), 3.40 (d, *J* = 13.6 Hz, 1H), 3.12 (dd, *J* = 12.3, 6.2 Hz, 1H), 2.0 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$): 142.3, 129.1, 128.2, 126.6, 124.3, 115.0, 59.0, 55.4, 41.0, 15.2. **HRMS (ESI+)**: calculated for $C_{12}H_{15}NNa$ (M^++Na): 197.0998 found: 197.0989. The enantiomeric excess was determined by HPLC using Chiralpak-IC-3-3-30 column [Hexane/Isopropanol (97:3), 3 mL/min]: τ_{major} = 2.86 min, τ_{minor} =3.14 min, (99% *ee*).

3.6. Water effects

Table 3. Study of water as the additive of the reaction.

Equiv. Water	Conv. (24h)	*d.r*	Ee (%)
1	16	50:50	99
5	45	99:1	99
10	n.r	-	-

[a] Conditions: **1** (0.3 mmol), **2** (0.1 mmol), **4f** (20 mol %) and H_2O (X equiv.) in DCE (0.3 mL) at rt for 24-48 h. [b] Conversion measured by ^{1}H-NMR.

We set up three different reactions in order to test the water effects on the conversion, diastero and enatioselectivity. The *trans*-beta-nitrostyrene **2a** (0.1 mmol, 1.0 eq.) and *N*-[(1*R*,2*R*)-2-(1-piperidinyl)cyclohexyl]-*N*′-[4-(trifluoromethyl)phenyl]squaramide (20 mol %) were dissolved in 0.3 ml of dichloroethane. Then, 3 equiv. of the 1-(trimethylsiloxy)-1,3-butadiene **1A** and different equiv. of water were added to the previous solution. The resulting mixture was stirred at room temperature.

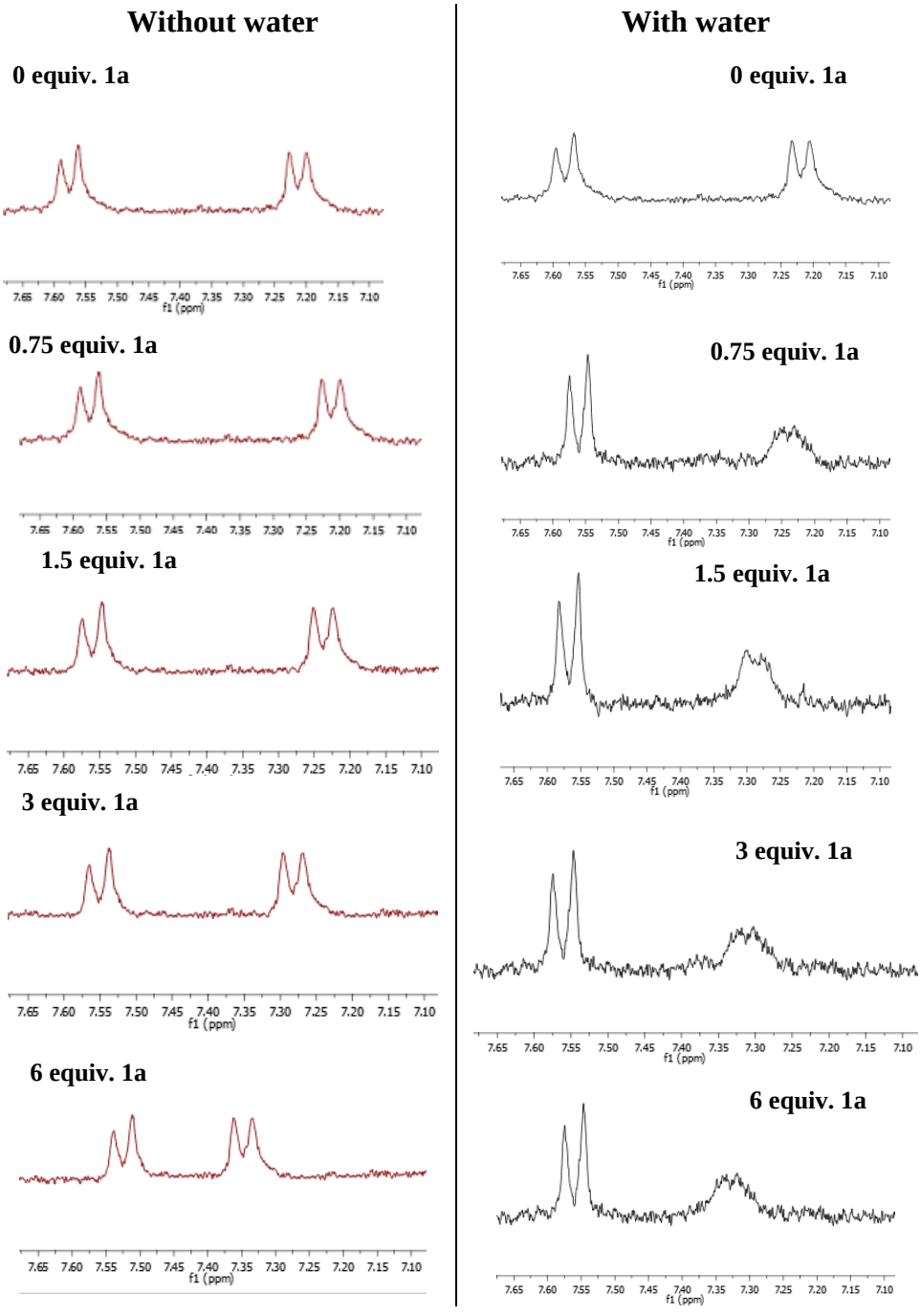
3.7. Binding studies

For the preparation of the NMR-Titration three stock solutions where prepared. On the one Hand a 0.0125 M solution of the bifunctional squaramide **4f** (Host). On the other hand two solutions of silyl-dienol ether **1a** (Guest), one with a molarity of 0.1, the other with a molarity of 0.01. A fixed amount of 400 µL host solution where added in each NMR-tube. The guest solution where added consecutively. All in all four NMR-tubes where prepared ending up with 6.0 equivalents of the guest (equivalents: 0.0, 1.5, 3.0, 6.0), compared to the host-molarity (Figure 18).

After this every NMR-tube was filled up to a total volumina of 1000 µL to end up with a host-concentration of 0.005 M. These experiments were carried out in the absence and presence (equivalents: 0.0, 2.5, 5.0, 10.0) of water.

For clarity, only the aromatic part of the bifunctional catalyst **4f** is shown in the NMR tritation.

Table 4. NMR Titration.



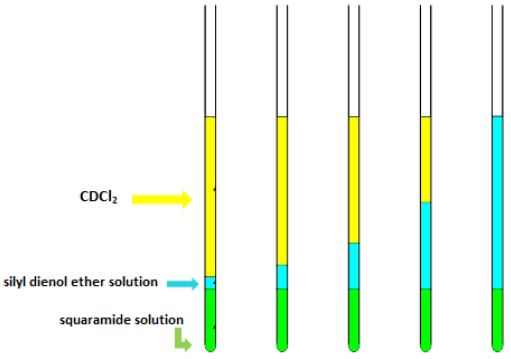


Figure 18. NMR tube for the titration.

3.8. Kinetic studies.

In order to determine the K.I.E value, we carried out two parallel reactions.

a) The first one: The trans-beta-nitrostyrene **2a** (0.1 mmol, 1.0 eq.) and N-[(1*R*,2*R*)-2-(1-piperidinyl)cyclohexyl]-N′-[4-(trifluoromethyl)phenyl]squaramide **4f** (10 mol %) were dissolved in 0.3 ml of dichloroethane. Then, 3 equiv. of the 1-(trimethylsiloxy)-1,3-butadiene **1A** and 10 µl of water were added to the previous solution. The resulting mixture was stirred at room temperature.

b) The second one: The trans-beta-nitrostyrene **2a** (0.1 mmol, 1.0 eq.) and N-[(1*R*,2*R*)-2-(1-piperidinyl)cyclohexyl]-N′-[4-(trifluoromethyl)phenyl]squaramide **4f** (10 mol %) were dissolved in 0.3 ml of dichloroethane. Then, 3 equiv. of the corresponding 1-(trimethylsiloxy)-1,3-butadiene **1A** and 10 µl of D_2O were added to the previous solution. The resulting mixture was stirred at room temperature.

Every two hours we took an aliquote and we checked the conversion by **^{1}H NMR** until 10 hours of reaction.

3.9. Computational methods.

Quantum chemistry calculations were carried out using the density functional theory (DFT). For the squaramide bifunctional catalyst we considered a simplified structure in which the CF_3 group in the benzene ring was substituted by a hydrogen atom, and the six-membered ring cycle NC_5H_{10} was modeled as $N(CH_3)_2$. Such simplifications decreased the computational costs by decreasing the number of basis functions and avoiding dealing with conformational equilibrium in NC_5H_{10} ring. In particular, geometry optimizations were performed using the M06-2_X functional in combination with the 6-31 + G(p,d) basis set including dichloroethane (ε = 10.4) solvent effects with the solvation model density (SMD). Harmonic vibrational frequencies have been also evaluated at the same level of theory to characterize minima and transition states in the potential energy surface. Transition states have been connected to products by optimization of geometries slightly modified from the transition states. All the calculations were performed using the Gaussian09 program.

The energies in the energetic profiles in the main text are given in kcal/mol.

The energies of the structures are given in hartree/particle.

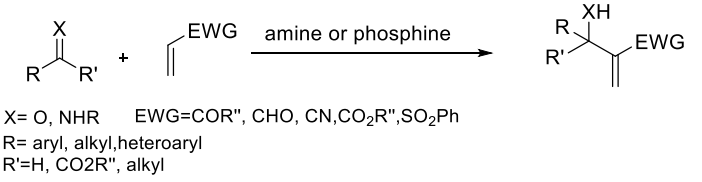
Chapter 4

A General Asymmetric Formal Synthesis of Aza-Baylis-Hillman Type Products under Bifunctional Catalysis

4.1. Introduction and Background.

The asymmetric aza-Baylis-Hillman reaction (aza-BHR)[1] represents the most straightforward methodology for the synthesis of chiral allylic amines, which have been used as starting materials or as a building blocks for the synthesis of different pharmaceutical and natural products.[2]

It was in 1968 when Morita first described the addition of an α, β-unsaturated carbonyl compound to an electrophile catalysed by a phosphine. Four years later Baylis-Hillman reported the same reaction, but this time under the influence of an amine catalyst. For this reason the reaction was named Morita-Baylis Hillman when the carbonyl compound was an aldehyde, and aza-Morita-Baylis Hilmann when an imine was involved as a electrophile (Scheme 1).[3]



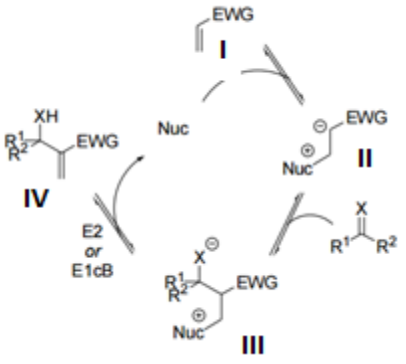
Scheme 1. Morita Baylis Hillman reaction.

It was Hoffman who first proposed a mechanism for the MBH reaction. The first reaction step starts with the 1,4-addition of the catalytic tertiary amine to the activated alkene to generate the zwitterionic aza-enolate **II**. In the second step, this enolate is added to the electrophile (amine or aldehyde). The third step involves an intramolecular proton shift (**III**), which subsequently generates the final MBH adduct (**IV**), and releases the catalyst via E_2 elimination (Scheme 2).

[1] For specific review on asymmetric Aza-Morita Baylis-Hillman see: a) F. L. Hu, M. Shi, *Org. Chem. Front*. **2014**, *1*, 587. b) H. Pellissier, *Tetrahedron*, **2017**, *73*, 2831.

[2] For general reviews on the aza-Morita Baylis Hillman see: a) D. Basavaiah, T. Satyanarayana, A. J. Rao, *Chem. Rev*., **2003**, *103*, 811. b) Y. Wei, M. Shi, *Chem. Rev*. **2013**, *113*, 6659. c) Y. Wei, M. Shi, *Eur. J. Org. Chem*. **2007**, 2905. d) D. Basavaiah, B. S. Reddy, S. S. Badsara, *Chem. Rev*. **2010**, *110*, 5447. e)) P. Xie, Y. Huang, *Org. Biomol. Chem*., **2015**, *13*, 8578. f) Y. Iwabuchi, S. J. Hatakeyama, *Synth. Org. Chem. Japan*, **2002**, *60*, 2.

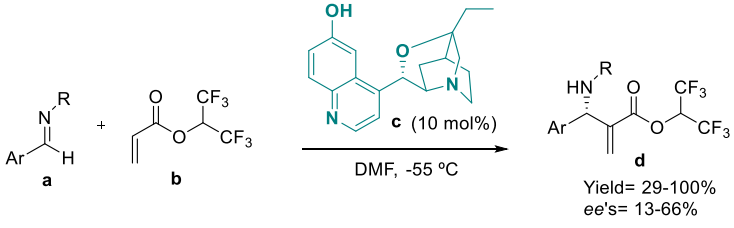
[3] a) K. I. Morita, Z. Suzuki, H. Hirose, *Bull. Chem. Soc. Jpn*. **1968**, *41*, 2815. b) A. B. Baylis, M. E. D. Hillman, *Chem. Abstr*. **1972**, *77*, 34174.



Scheme 2. Mechanistic proposal for the MBH reaction.

Even though this is a well-known reaction, only few examples in the asymmetric field have been reported and most of these are related to the use of non-substituted double bonds in the presence of vinyl ketones and esters as EWGs.[4] In the following lines we are going to highlight some of the most relevant organocatalyzed examples described in the literature.[5]

Hatakeyama and co-workers[6] in 2003 presented a novel methodology for the preparation of aryl-substituted α-methylene β-amino acid type products through an aza-MBH reaction between diphenylphosphinoyl imines and HFIPA (1,1,1,3,3,3-hexafluoroisopropylacrylate). However, the desired products were obtained with low-moderate enantioselectivities (Scheme 3).



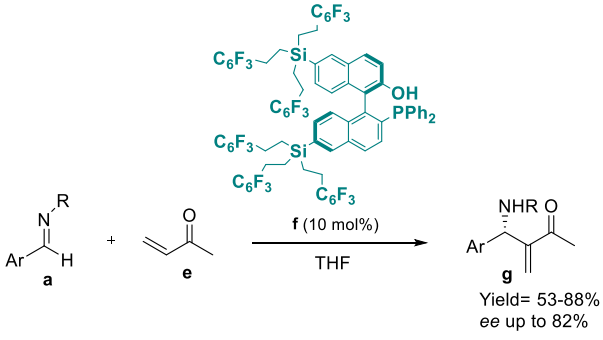
Scheme 3. Enantioselective Aza-MBH with HFIPA.

[4] For metalcatalyzed asymmetric MBH, see: a) K. Hyodo, S. Nakamura, N. Shibata, *Angew. Chem. Int. Ed.* **2012**, *51*, 10337. b) T. Yukawa, B. Seelig, Y. Xu, H. Morimoto, S. Matsunaga, A. Berkessel, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 11988.

[5] For other Works see: a) J. Wang, H. Li, L. Zu, W. Wang, *Org. Lett*, **2005**, *7*, 4293. b) H. Song, K. Yuan, X. Wu, *Chem. Commun*, **2011**, *47*, 1012. c) Y. Yao, J. Li, Q. Zhou, L. Dong, Y. Chen, *Chem. Eur. J*. **2013**, *19*, 9447.

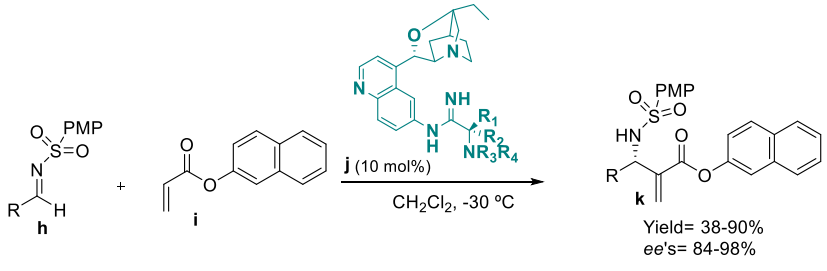
[6] S. Kawahara, A. Nakano, T. Esumi, Y. Iwabuchi, S. Hatakeyama, *Org. Lett*. **2003**, *5*, 3103.

The group of Shi have reported different examples of aza-Baylis-Hillman reactions using tosylimines.[7] An asymmetric aza-MBH reaction between *N*-sulfonated imines and methyl vinyl ketone under the catalysis of a chiral phosphine Lewis base was shown. This catalyst albeit in its structure two perfluoroalkane chains at the 6,6' positions of the naphthalene core. The desired products were obtained with moderate yields and enantioselectivities up to 82% *ee* (Scheme 4).



Scheme 4. Methodology described by Shi and co-workers.

Masson's group[8] in 2008 developed a new strategy for the enantioselective aza-MBH reaction employing an effective dual catalysts **j**. A combination of β-napthol and a bifunctional catalyst derived from β-ICD results on the access to α-methylene-β-amino-β-alkyl carbonyl compounds **k** with good yields and enantioselectivities (Scheme 5).

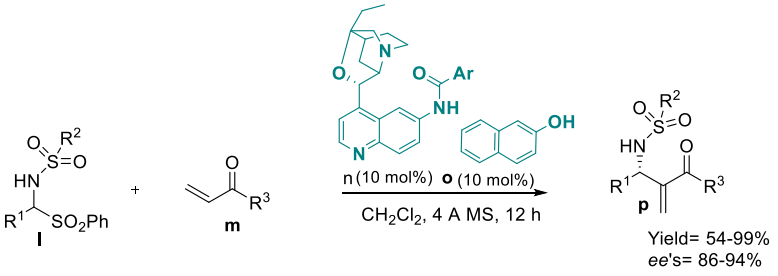


Scheme 5. Synthesis of α-methylene-β-amino-β-alkyl carbonyl compounds.

[7] a) M. Shi, Y. M. Xu, *Angew. Chem. Int. Ed*. **2002**, *41*, 2507. b) M. Shi, L. H. Chen, C. Q. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3790. c) M. Shi, Y. M. Xu, Y. L. Shi, *Chem. Eur. J.* **2005**, *11*, 1794. d) M. Shi, L. H. Chen, W. D. Teng, *Adv. Synth. Catal*. **2005**, *347*, 1781.

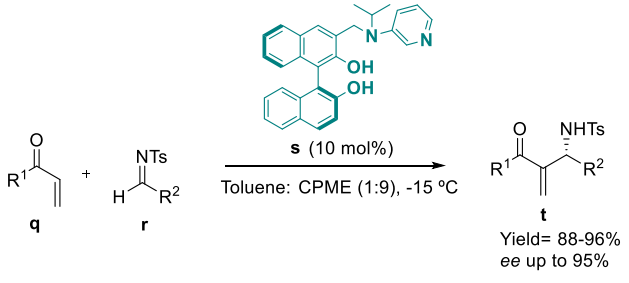
[8] a) N. Abermil, G. Masson, J. Zhu, *J. Am. Chem. Soc*, **2008**, *130*, 12596. b) N. Abermil, G. Masson, J. Zhu, *Org. Lett*, **2009**, *11*, 4648.

Moreover, two years later, the same group published another variant of the Aza-MBH reaction, but this time using α-amido-sulfones. The same dual catalyst employed in the previous work, was needed for both, the *in situ* generation of *N*-sulfonylimine, and to initiate the reaction. The corresponding products **p** were isolated with high yields as well as good enantioselectivities (Scheme 6).[9]



Scheme 6. Aza-MBH with α-amido-sulfones under a dual catalyst system.

In 2005, Sasai *et. al* [10]established a new asymmetric aza-MBH reaction catalyzed for the first time by a BINOL derivatives (Scheme 7). This system efficiently promoted the reaction between *N*-tosylimine **r** and methyl vinyl ketone **q**, in order to obtain the corresponding products **t** with excellent yields and enantioselectivities up to 95% (Scheme 7).

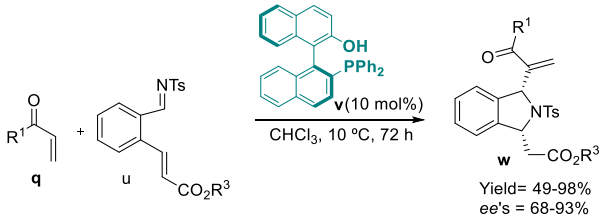


Scheme 7. Aza-MBH catalyzed by BINOL derivative.

Five years later the same group described an enantioselective aza-MBH domino process. The reaction of deficient alkenes **q** and *N*-tosylimines derivatives **u** is

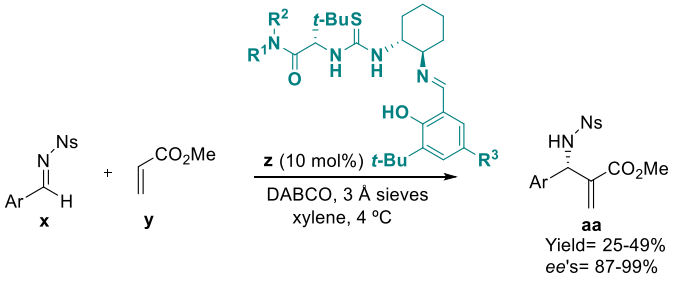
[9] N. Abermil, G. Masson, J. Zhu, *Adv. Synth. Catal*., **2010**, *352*, 656.
[10] a) K. Matsui, S. Takizawa, H. Sasai, *J. Am. Chem. Soc.* **2005**, *127*, 3680. f) S. Takizawa, N. Inoue, S. Hirata, H. Sasai, *Angew. Chem. Int. Ed*. **2010**, *49*, 9725.

promoted by a chiral acid-base organocatalyst, obtaining the desired 1,3-disubstituted isoindolines **w** with high diastereo- and enantioselectivities (Scheme 8).



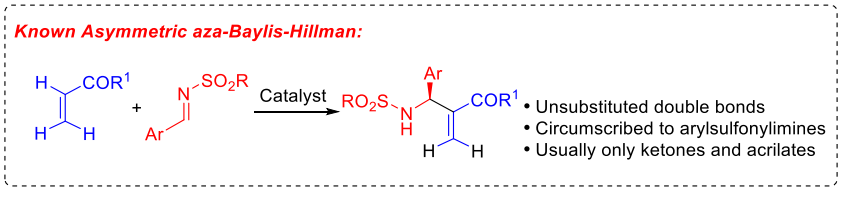
Scheme 8. Aza-MBH domino reaction published by Sasai's group.

Jacobsen's group[11] in 2005, described an asymmetric aza-MBH reaction of nosylimines **x** with methyl acrylate **y** under bifunctional catalysis **z**. Even though the yields were quite moderate, the enantioselectivities for a wide range of aromatic imines were unprecedented for this type of reaction (Scheme 9).



Scheme 9. Enantioselective aza-MBH under bifunctional catalysis.

All these examples have shown that the reaction can only take place with non-substituted double bonds and mostly with ketone and esters as EWG of the double bond (e.g. acrylates or vinylmethyl ketones; Scheme 10).

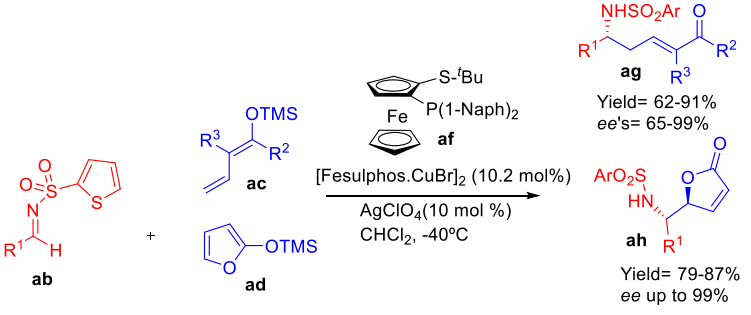


Scheme 10. Known Asymmetric aza-Baylis-Hillman reaction.

[11] I. Raheem, E. Jacobsen, *Adv. Synth. Catal.* **2005**, *347*, 1701.

The lack of reactivity of the mono-β-substituted and β,β-disubstituted double bonds makes the synthesis of these enantioenriched tri- and tetra-substituted double bonds with different electron withdrawing groups in the Baylis-Hillman reaction difficult. In addition, most of these examples have employed aryl-tosylimines as the starting material, where alkyl imines or ketimines were unreactive, or led to moderate enantioselectivities.

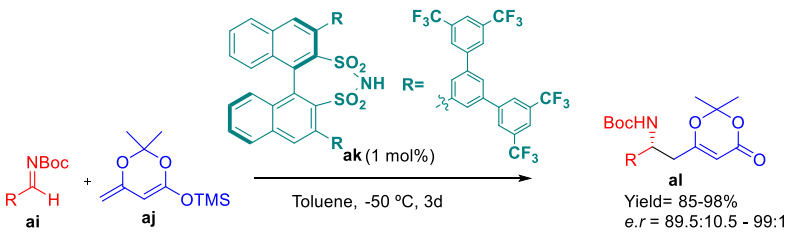
On the other hand, in 2008 Carretero´s[12] group showed an elegant metal catalyzed methodology to functionalize the 1,5 position of both cyclic and acyclic silyldienolate derivatives (**ac**,**ad**) through a vinylogous Mukaiyama-Mannich reaction. This work involves the use of *N*-2-thienylsulfonylimines and a copper (I) complexes of Fesulphos ligands **af** to promote the reaction. Both final products (**ag** and **ah**) were obtained with high yields and enantioselectivities (Scheme 11).



Scheme 11. Vinylogous Mukaiyama-Mannich reaction described by Carretero's group.

More recently, List group[13] have employed chiral disulfonimides **ak** as the effective catalysts to perform the asymmetric vinylogous Mukaiyama Mannich reaction between *N*-Boc imines **al** and silyl-dienol ethers **aj** under disulfonimide catalysis, with high yields and enantioselectivities (Scheme 12).

[12] A. Salvador Gonzalez, R. Gomez Arrayas, M. Rodrihuez Rivero, J. C. Carretero, *Org. Lett*, **2008**, *10*, 4335.
[13] Q. Wang, M. Gemmeren, B. List, *Angew. Chem. Int. Ed.* **2014**, *53*, 13592.



Scheme 12. Chiral disulfonimide as effective catalyst for the aza-MBH.

These remarkable examples showed that final aldehydes and esters can be selectivity funcionalized at the 1,5 positions from moderate to good enantioselectivies. The orbital coefficients and electrophilic susceptibility are mainly responsible for this reactivity[14] provoking the observed 1,5 nucleophilic attack.

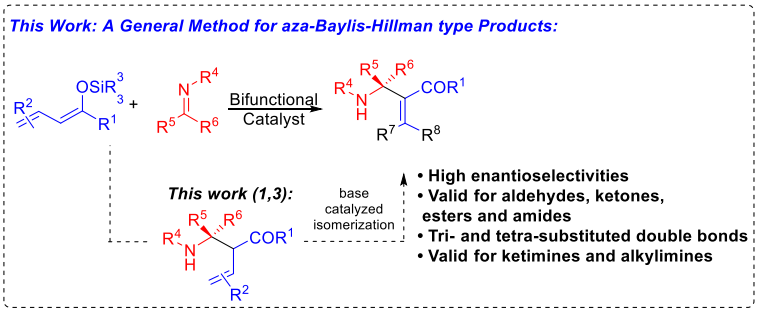
4.2. Objectives.

In the previous chapter, our group has shown that 1,5- can be easily switched to 1,3-funcionalization using bifunctional catalysis. This provokes a dramatic change in the regioselectivity, from the 1,5 to the 1,3-functionalization.[15] This variation enables the 1,3 addition of silyl-dienol ethers to nitroalkenes for the synthesis of tri- and tetra-substituted double bonds in Rauhut-Currier type products.

We hypothesized that if instead of a nitroalkene, we could use an imine as electrophile in/or similar conditions. If the regioselectivity remains 1,3 and it is followed by the isomerization of the double bond of the intermediate, we would have access to the Baylis-Hillman type products, which are excellent building blocks for the synthesis of complex molecules. With all these precedents on mind, we set as the main goal of this chapter, the development of a general method, for the formal synthesis of aza-Baylis-Hillman products, involving the addition of silyl-dienol ethers to imines, catalyzed by bifunctional (Scheme 13).

[14] For reviews of organocatalytic vinylogous aldol reactions see: a) S. Denmark, E. J. R. Heemstra, G. L. Beutner, *Angew. Chem. Int. Ed.* **2005**, *44*, 4682. b) S. V. Pansare, E. K. Paul, E. K. *Chem. Eur. J.* **2011**, *17*, 8770. c) V. Bisai, *Synthesis*, **2012**, *44*, 1453.

[15] M. Frias, R. Mas-Ballesté, S. Arias, C. Alvarado, J. Alemán, *J. Am. Chem. Soc*. **2017**, *139*, 672.



Scheme 13. Main objective of this chapter.

4.3. Results and Discussion.

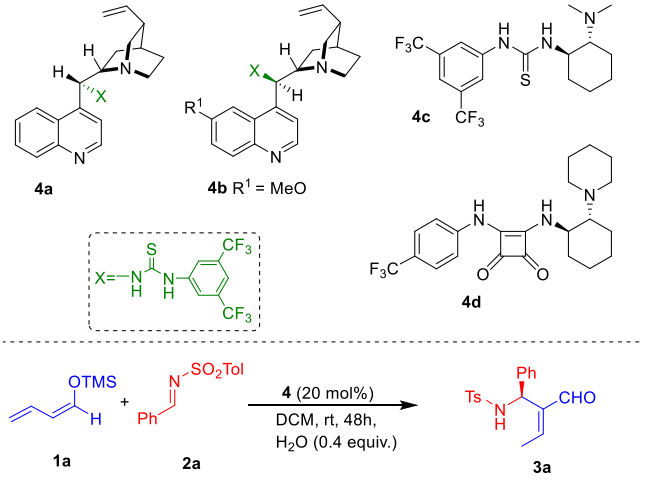
4.3.1. Screening of the reaction conditions.

Firstly, we studied the reaction of the silyldienolether **1a** with tosylimine **2a** and different thiourea and squaramide bifunctional catalysts **4a-d** (Table 1). As in the previous chapter, in all cases we only observed the 1,3-regioselectivity was observed.

All the catalysts **4a-d** showed full conversion in the presence of 0.4 equiv. of water. However, Takemoto´s catalysts **4c** showed the best enantioselectivity (entry 3). Then, different solvents were studied (entries 5-8), decreasing the reactivity and the enantioselectivity compared to dichloromethane under the **4c** catalysis.

In view of these moderate results, we decided to investigate different imines **2a-g** (Table 2).

Table 1. Optimization of reaction conditions and catalyst for the aza-BHR.[a]



Entry	Catalyst (mol%)	Solvent	Ee[b] (%)	Conv.(%)[c]
1	**4a** (20 mol%)	CH_2Cl_2	20	100
2	**4b** (20 mol%)	CH_2Cl_2	46	100
3	**4c** (20 mol%)	CH_2Cl_2	50	100
4	**4d** (20 mol%)	CH_2Cl_2	28	100
5	**4c** (20 mol%)	HFB	42	46
6	**4c** (20 mol%)	DCE	44	70
7	**4c** (20 mol%)	MeCN	30	55
8	**4c** (20 mol%)	THF	49	86

[a] All the reactions were performed in 0.1 mmol scale in 1.0 mL solvent. [b] Determined by SFC chromatography. [c] Determined by ^{1}H NMR analysis of the crude mixture after 48 hours.

When pyridylsulfonylimine **2b**[16] was used, a moderate enantioselectivity was found (entry 2), whereas the other bulkier imines such as **2c** and **2d** gave a lower conversion and worse enantioselectivities (entries 3 and 4, Table 2). The use of a sulfonyl group with an electron-donanting group such as **2e** did not improve the results (entry 5, Table 2) and Boc-imine **2f** did not afford any conversion to the desired product (entry 6, Table 2).

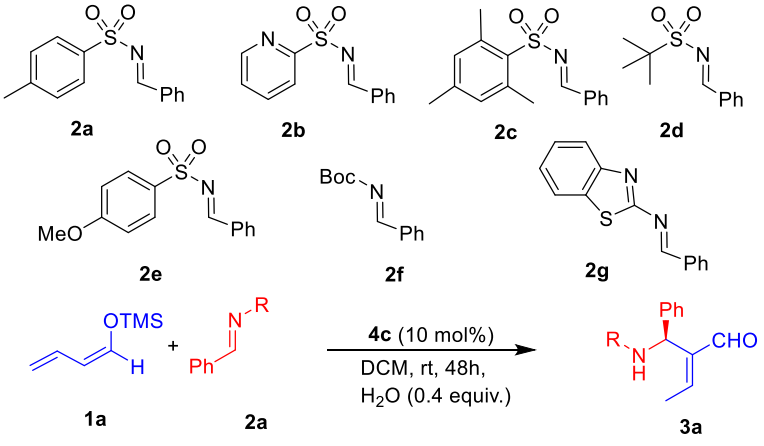
All these imines (**2a-2e**) have a moderate capability of forming a hydrogen bond with Takemoto´s catalyst **4c** because the sulfonyl group weakens the availability of the lone pair on the nitrogen (C=N:). Thus, we hypothesized that a more hydrogen coordinated imine such as **2g**[17] would increase the enantiomeric excess. Pleasantly, the reaction of imine **2g** led to the final product **3g** with the highest enantiomeric excess (>99 % ee, entry 7) with a moderate conversion of 67 % due to the lower reactivity of this imine compared with the sulfonyl-imines.

[16] See for example: a) S. Nakamura, H. Nakashima, H. Sugimoto, H. Sano, M. Hattori, N. Shibata, T. Toru, *Chem. Eur. J.* **2008**, *14*, 2145. b) J. Esquivias, R. Gomez Arrayas, J. C. Carretero, *J. Org. Chem.*, **2005**, *70*, 7451.

[17] H. Xiao, W. Yang, D. Du, *Adv.Synth.Catal.* **2013**, *355*, 1137.

In order to increase the conversion we studied the influence of different quantities of water (entries 8-10). We determined that 4.5 equivalents of water were needed to obtain a full conversion after 24 hours. When a water free reaction was carried out only 7 % conversion was obtained (entry 12) and the use of 1.5 and 3 equivalents did not afford full conversions after 24 h (entries 8 and 9). The amount of catalyst was reduced to 10 mol % with the same result but with a slightly longer reaction time of 48 h (entry 11).

Table 2. Different imines for the aza-BHR under bifunctional catalysis.[a]



Entry	Imine	Water [eq.]	Ee[b] (%)	Time (h)	Conv.(%)[c]
1	**2a**	0.4	50	48	100
2	**2b**	0.4	53	48	100
3	**2c**	0.4	n.d	48	22
4	**2d**	0.4	12	48	61
5	**2c**	0.4	48	48	46
6	**2f**	0.4	-	48	n.r.
7	**2g**	0.4	>99	48	67
8	**2g**	1.5	>99	24 (48)	22 (51)[d]
9	**2g**	3	>99	24 (48)	58 (100) [d]
10	**2g**	4.5	>99	24	100
11	**2g**	4.5	>99	48	100
12	**2g**	-	-	48	7

[a] All the reactions were performed in 0.1 mmol scale in 1.0 mL solvent. [b] Determined by SFC chromatography. [c] Determined by ^{1}H NMR analysis of the crude mixture after 24 or 48 hours. [d] Conversion after 48 h in brackets. [e]10 mol% of catalyst **4c**.

Under these optimized conditions the scope of the reaction using different imines **2** (Table 3) and silyl reagents **1** (Schemes 2 and 3) was carried out (See next section).

4.3.2. Scope of the reaction.

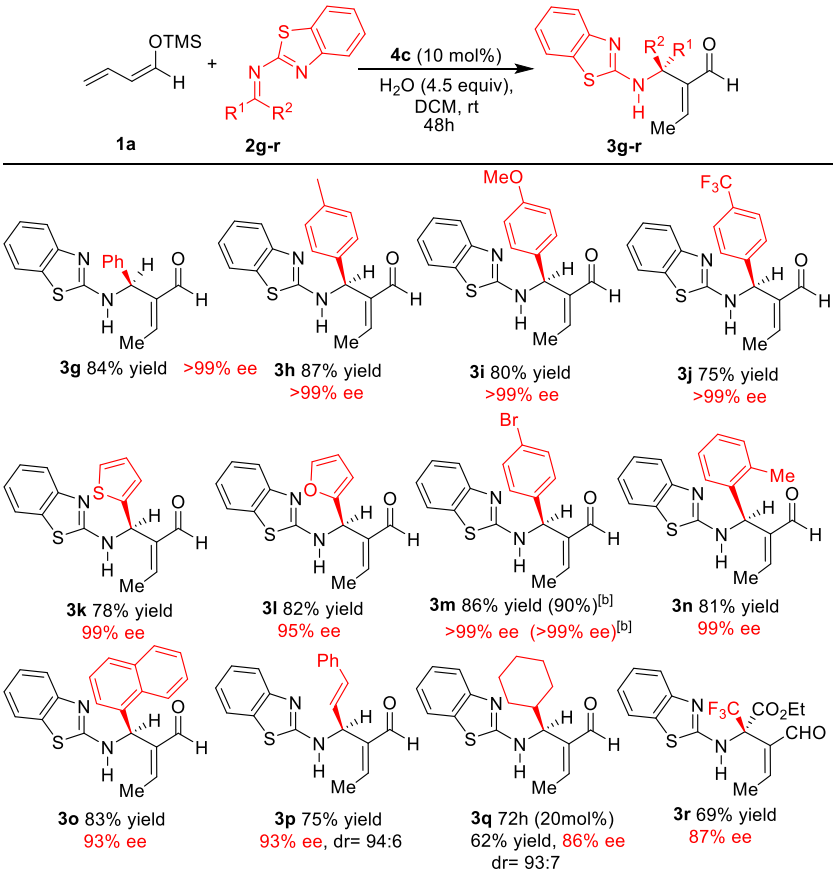
Different electron donating groups (*p*-Me, *p*-MeO **2h**, **2i**) or electron withdrawing groups (*p*-CF3, **2j**) worked with excellent enantioselectivies (all examples; >99% ee). Heteroaromatic groups such as thienyl or furyl moieties also afforded aza-BHR products with good to excellent enantioselectivities (95-99 % ee, **2k-l**).

Bromo (**2m**), and the bulkier substituents such as **2n** and **2o** were also tolerated under these conditions, providing **3m**, **3n** and **3o** with good ee`s. The reaction was scale up (1.2 mmol) with the bromo derivative **3m** with a similar yield and enantioselectivity (result between brackets).

A double bond such as imine **2p** or an alkyl imine such as **2q** also led to the corresponding adducts (**3p** and **3q**) under these catalytic conditions which are difficult to obtain with the standard aza-BHR, with a slightly lower *Z*/*E* selectivity (dr= 94:6 and 93:7).

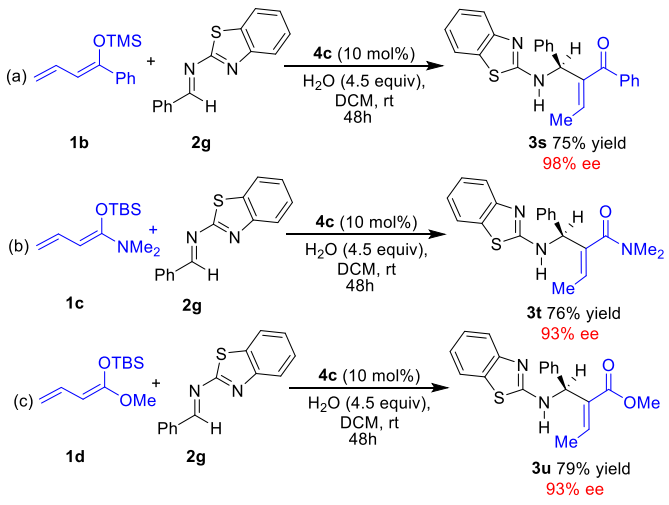
In addition, the more challenging ketimine **2r** was also studied and afforded the optically enriched quaternary center product **3r** in a good yield and enantioselectivity.

Table 3. Scope of the aza-BHR with different imines **2a-n**.[a]



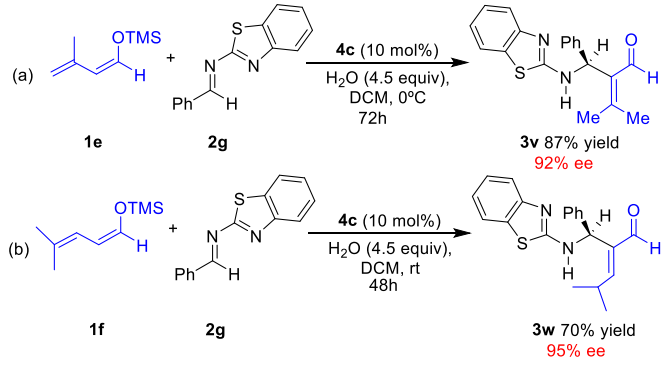
[a] Conditions: 1 (0.3 mmol), 2 (0.1 mmol), **4c** (10 mol %) and H_2O (4.5 equiv.) in DCM (0.3 mL) at rt after 48 h.[b] Reaction carried out at 1.2 mmol scale.

The reaction also tolerated different groups at the α position to the TMSO group at the silyl-dienol ether **1b-d** (Scheme 14). Therefore, the phenyl group led to the ketone **3s** with an excellent enantioselectivity (equation a), whereas the use of enolate **1c** afforded the amide **3t** in an excellent yield and enantioselectivity (equation b) which cannot be obtained under the standard aza-Baylis-Hillman reaction conditions due to the low electrophilic character of the double bond. In a similar manner, the silyl reagent **1d** reacted with the imine **2g** to give the ester **3u** with excellent *ee* and yield (equation c).



Scheme 14. Synthesis of ester, ketone and amide aza-BH type products.

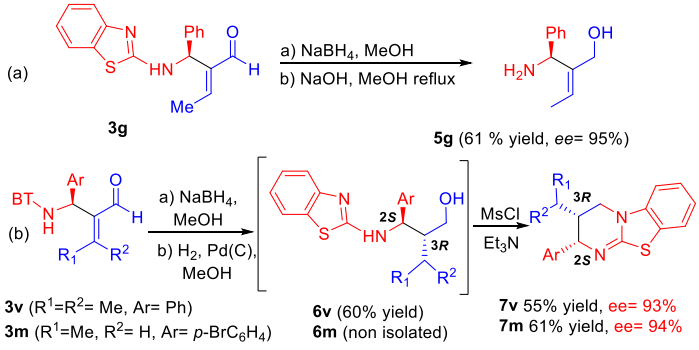
The substitution at the 4 and 5-positions of the silyl-enol-ether (**1e** and **1f,** Scheme 15) led to the β,β-disubstituted **3v** and β-monosubstituted **3w** adducts respectively in good yields and enantioselectivies. It is remarkable that it is not possible to obtain these enantio-enriched adducts using other methods described in the literature.



Scheme 15. Different substitution at the silyl-dienol ethers for the synthesis of tri and tetrasubstituted aza-BHR type products.

Finally, we carried out different transformations of the adducts obtained to synthesize privileged compounds. Therefore, the benzothiazole group could be easily removed after reduction of the aldehyde **3g** and subsequent hydrolysis in basic conditions, giving the 1,3-aminoalcohol **5g** with a significance loss of

enantioselectivity (equation a, Scheme 16), which can be used as precursor for a large number of pharmaceutical products.[18] Moreover, our methodology also provided the possibility of synthetize privileged structures such as catalysts **7v** and **7m** that have been previously used as Lewis super-bases[19] (equation b, Scheme 16). The procedure started with the reduction of **3v** and **3m** to give **6v** and **6m**, which after reduction of the double bond, the cyclization afforded the catalysts **7v** and **7m**.



Scheme 16. Derivatization of tri- and tetra-substituted aza-BHR type products (BT= benzothiazole).

The absolute configuration of Baylis-Hillman products **3** were assigned by correlation with known compounds in the literature (**6v** and **7v**)[19] and were determined as 2*S* and 3*R*, whereas the configuration of the double bond was determined as *E* by n.O.e. NMR experiments (Figure 1, 2 and 3).

[18] a) C. Yao, Z. Xiao, X. Ning, J. Liu, Y. Kang, Org. Lett, 2014, 16, 5284. b) S. Lait, D. Rankic, B. Keay, *Chem. Rev.* **2007**, *107*, 767.

[19] a) L. C. Morrill, T. Lebl, A. M. Z. Slawina, A. D. Smith, *Chem. Sci.*, **2012**, *3*, 2088.b) C. Joannesse, C. P. Johnston, C. Concell´on, C. Simal, D. Philp, A. D. Smith, *Angew. Chem., Int. Ed*., **2009**, *48*, 8914; c) A. Matviitsuk, M. D. Greenhalgh, D. Barrios Antúnez, A. M. Z. Slawin, A. D. Smith, *Angew. Chem. Int. Ed*. **2017**, *56*,

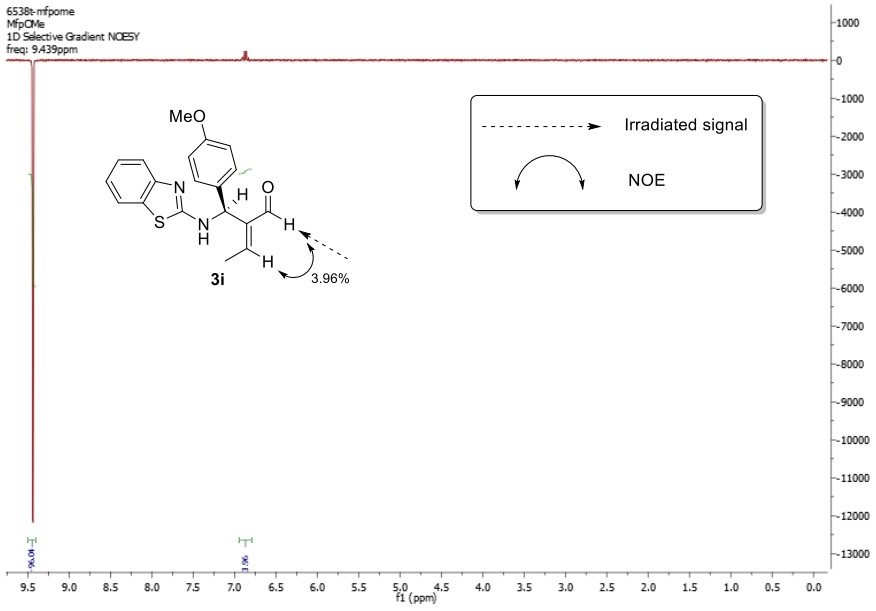


Figure 1. n.O.e NMR spectrum.

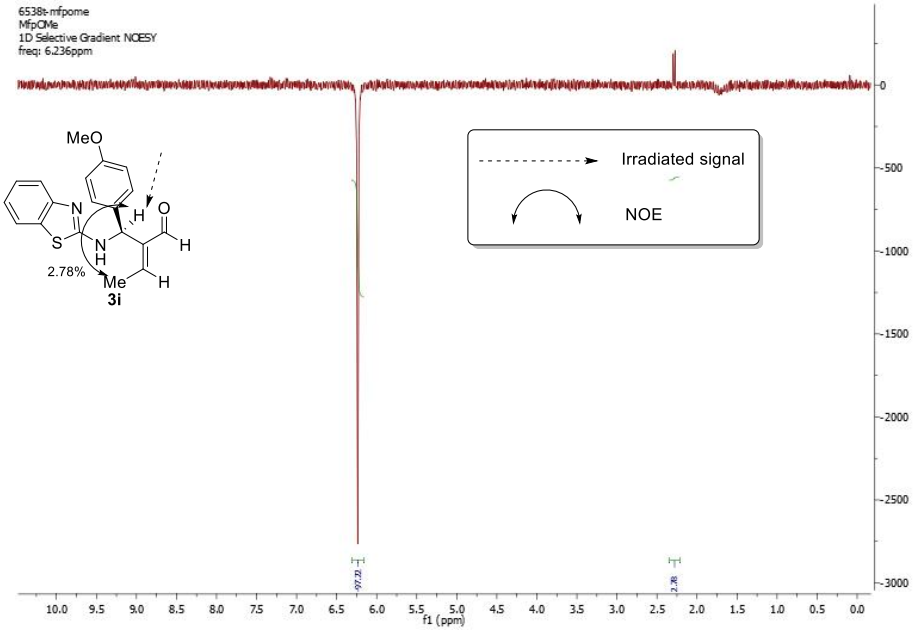


Figure 2. n.O.e NMR spectrum.

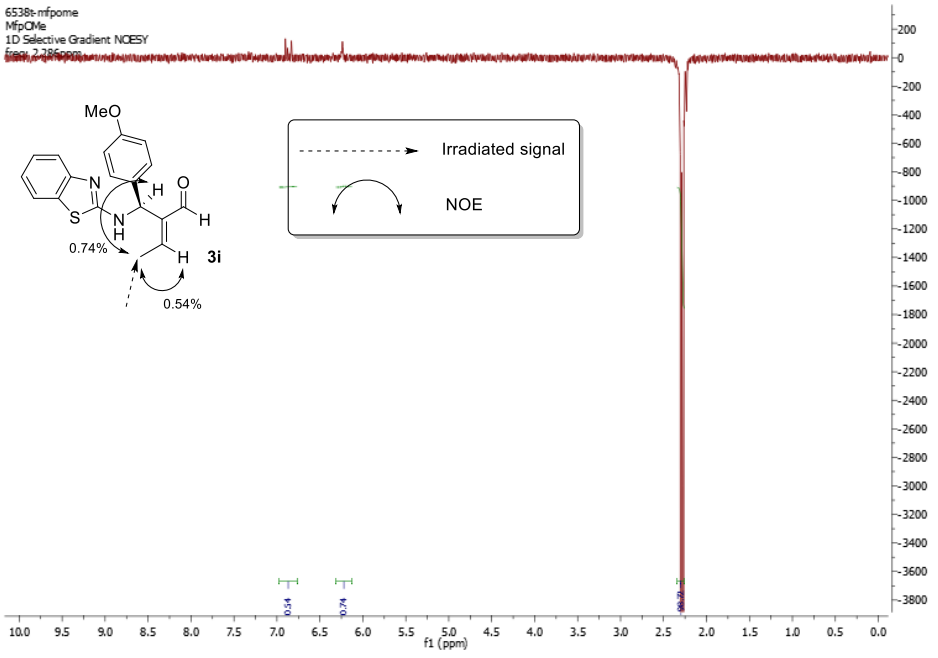


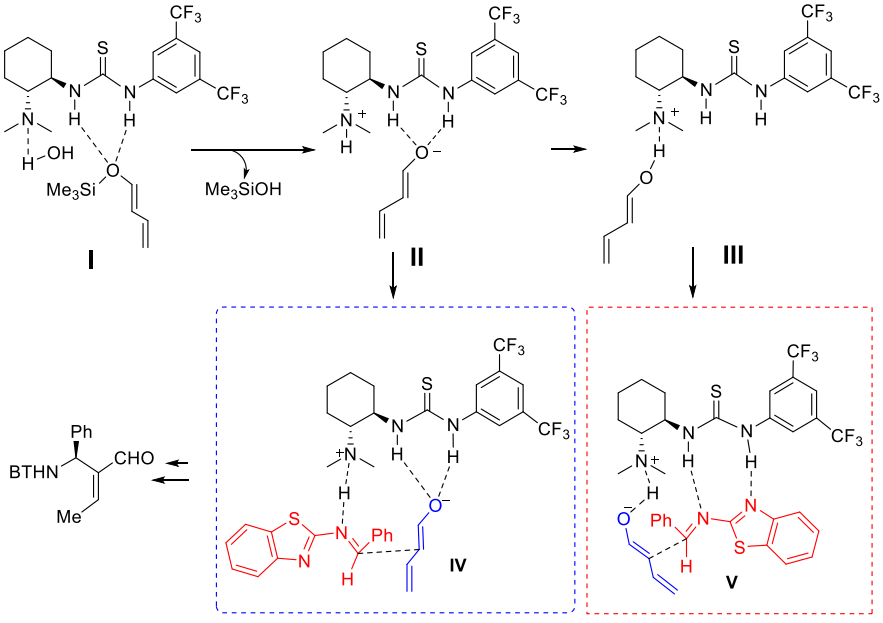
Figure 3. n.O.e NMR spectrum.

4.4. Mechanistic proposal.

Based on our previous calculations[15] and the additional experimental data obtained in this work (see below), a proposed mechanism is outlined in Scheme 17.

A water molecule can easily attack the Si center (**I**) and further evolution of this system implies firstly a proton transfer from the water molecule to the amine nitrogen, followed by a nucleophilic attack of the resulting hydroxide to the silicon atom. After the hydrolysis step, two intermediates before the coordination to the imine can be postulated (**II** and **III**). The hydrogen bond formation with the imine **2** leads to the intermediate **IV** or **V**. Intermediate **V** is based on Takemoto´s model,[20] in which the coordination with the electrophile, in this case the imine **2a**, is taking place through the thiourea moiety. By contrast, the intermediate **IV** is based on the well-known Papai model.[21] Such pre-organization is characterized by the coordination of the electrophile through the ammonium salt, whereas the nucleophile can be strongly stabilized by the thiourea group.

[20] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc*. **2003**, *125*, 12672.
[21] A. Hamza, G. Schubert, T. Soos, I. Papai, *J. Am. Chem. Soc*. **2006**, *128*, 13151.

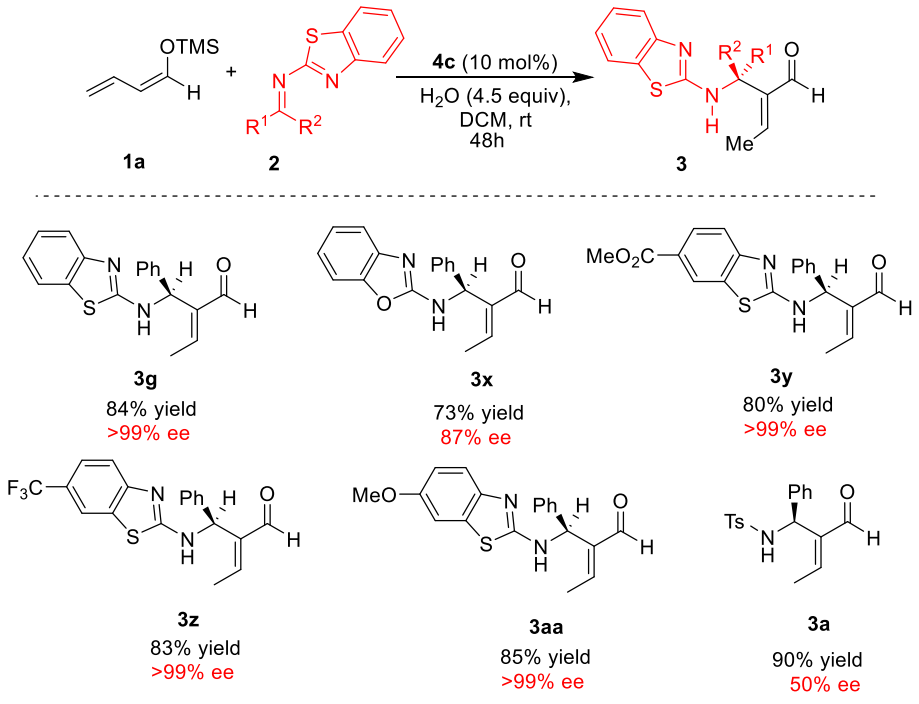


Scheme 17. Mechanistic proposal for the Aza-BHR.

In order to differentiate between these two models different imines **2** with different aromatic residues at the benzothiazole group were synthesized (Scheme 18). The use of different benzothiazole imines with EWG and EDGs were not found to have any influence of the enantioselectivity, and in all the cases high enantioselectivities, >99 % for products **3y**, **3z** and **3aa** were obtained. Therefore, the coordination of the benzothiazolinic nitrogen to the catalyst is implausible since no influence of the substitution at the para position to this nitrogen was found. Conversely, the use of imines with a strong electron-withdrawing character such as the tosyl group, provoke a dramatic decrease in the enantioselecitivy (**3a**, *ee* = 50 %). In addition, when a sulfur atom is substituted by one with a stronger electronegativity such as oxygen; benzo[d]oxazole, **3x**, the resultant enantioselectivity is also lower (*ee* = 87 %).

These last two results indicate that the key coordination hydrogen bond is the lone pair of the iminic nitrogen (C=N:), indicating that the more plausible mechanism is Papai's model,[20] where the dienolate is strongly stabilized by the thiourea moiety and

the imine is coordinated to the ammonium ion group (see **IV**). Then, after the addition (C-C bond formation) and isomerization of the double bond gives the final aza-Baylis-Hillman products with high enantioselectivity.



Scheme 18. Results obtained with different substitution at the benzothiazole core under standard conditions

4.5. Conclusions

In conclusion, a new organocatalytic strategy for the synthesis of enantioenriched aza-Baylis-Hillman type products via a frustrated vinylogous reaction is presented. This process proceeds under mild conditions with good yields and excellent enantioselectivities. The reaction tolerates a large number of different imines, and the synthesis of tri- and tetra-substituted aza-Baylis-Hillman type products. Moreover, easy derivatizations of the final products led to important building blocks in organic synthesis such as 1,3-aminoalcohols and Brønsted super-base catalysts. A mechanism for this reaction based on the experimental data has been proposed.

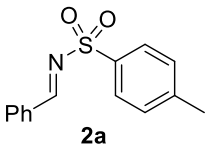
4.6. Experimental part

4.6.1. General Experimental Details

It was followed the general experimental details of section **1**. In addition all starting materials were purchased from commercial suppliers without further purification. Silyl-dienol ether **1a** was purchased in Sigma-Aldrich whereas **1b-1f** were synthesize according to the procedures described in the literature with light modifications.

4.6.2. Procedure for the synthesis of imines (2a-2v)

(*E*)-*N*-Benzylidene-4-methylbenzenesulfonamide (2a)[22]

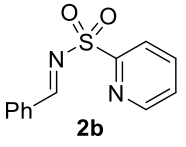


2a

To a solution of 4-methylbenzenesulfonamide (5.8 mmol, 1.0 eq.) in dry DCM (18.0 mL, 0.32 M) were added benzaldehyde (6.96 mmol, 1.2 eq.), molecular sieves of 4Å (1 g/mol) and 10 mol% of pyrrolidine (0.58 mmol, 10 mol%). The mixture was heated to reflux (60 ºC) in a seal vial during 24 h. The reaction mixture was filtrated through a pad of Celite and the filtrate was concentrated in vacuo. The product was obtained as a white solid, used without further purification and with spectroscopic data in accordance to the literature. (Yield= 99 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.97 – 7.86 (m, 4H), 7.62 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 2.44 (s, 3H).

(*E*)-*N*-Benzylidenepyridine-2-sulfonamide (2b)[23]



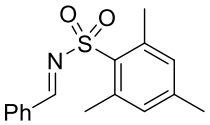
2b

To a solution of pyridine-2-sulfonamide (4.7 mmol, 1.0 eq.) in dry toluene (0.5 M) were added benzaldehyde (4.7 mmol, 1.0 eq.), molecular sieves of 4Å (800 mg/mmol) and Amberlite® 15 (0.016 mmol, 1.6 mol%). The mixture was heated to reflux (140 ºC) in a seal vial during 12 h. The reaction mixture was filtrated through a pad of Celite and the filtrate was concentrated in vacuo. The product was obtained as a yellow solid, used without further purification and with spectroscopic data in accordance to the literature. (Yield= 87 %).

[22] S. Morales, F.G. Guijarro, J.L. García Ruano, M.B. Cid, *J. Am. Chem. Soc*, **2014**, *136*, 1082.
[23] J. Esquivias, R. Gomez-Arrayás, J.C. Carretero, *Angew. Chem. Int. Ed*, **2006**, *45*, 629.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.70 (ddd, J = 4.6, 1.6, 0.8 Hz, 1H), 8.24 (dt, J = 1.7, 8.6 Hz, 1H), 8.02 – 7.93 (m, 3H), 7.64 (m, 2H), 7.60 – 7.45 (m, 2H).

(*E*)-*N*-Benzylidene-2,4,6-trimethylbenzenesulfonamide (2c)[24]

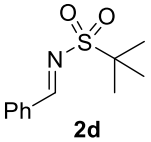


2c

To a solution of 2,4,6-trimethylbenzenesulfonamide (1.0 mmol, 1.0 eq.) in dry toluene (0.5 M) were added benzaldehyde (1.3 mmol, 1.3 eq.), molecular sieves of 4Å (800 mg/mmol) and Amberlite® 15 (0.016 mmol, 1.6 mol%). The mixture was heated to reflux (140 ºC) in a seal vial during 12 h. The reaction mixture was filtrated through a pad of Celite and the filtrate was concentrated in vacuo. The product was obtained as a yellow solid, used without further purification and with spectroscopic data in accordance to the literature. (Yield= 89 %).

^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.99 (s, 1H), 8.01 – 7.92 (m, 3H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 6.9 Hz, 1H), 7.00 (s, 2H), 2.67 (s, 6H), 2.30 (s, 3H).

(*E*)-*N*-Benzylidene-2-methylpropane-2-sulfonamide (2d)[25]



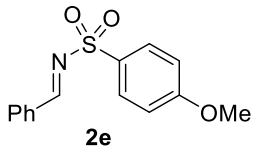
2d

To a solution of 2-methylpropane-2-sulfonamide (1.46 mmol, 1.0 eq.) in dry toluene (0.25 M) were added benzaldehyde (1.75 mmol, 1.2 eq.), molecular sieves of 4Å (800 mg/mmol) and Amberlite® 15 (0.01 mmol, 10 mol%). The mixture was heated to reflux (140 ºC) in a seal vial during 12h. The reaction mixture was filtrated through a pad of Celite and the filtrate was concentrated in vacuo. The product was obtained as a yellow solid, used without further purification and with spectroscopic data in accordance to the literature. (Yield= 85 %).

^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.97 (s, 1H), 7.94 (d, *J* = 7.1 Hz, 2H), 7.65 – 7.46 (m, 3H), 1.40 (s, 9H).

[24] K. S. Williamson, J. W. Sawickia, T.P. Yoon, *Chem. Sci*, **2014**, 5, 3524.
[25] Y. Morita, T. Yamamoto, H. Nagai, Y. Shimizu, M. Kanai, *J. Am. Chem. Soc*, **2015**, *137*, 7075.

(*E*)-*N*-Benzylidene-4-methoxybenzenesulfonamide (2e)[26]

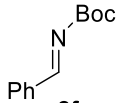


2e

To a solution of 4-methoxybenzenesulfonamide (1.0 mmol, 1.0 eq.) in dry toluene (0.5 M) were added benzaldehyde (1.3 mmol, 1.43 eq.) and $BF_3 \cdot OEt_2$ (0.10 mmol, 10 mol%). The mixture was heated to reflux (140 ºC) in a seal vial during 12 h. The reaction mixture was filtrated through a pad of Celite and the filtrate was concentrated in vacuo. The product was obtained as a white solid, used without further purification and with spectroscopic data in accordance to the literature. (Yield= 82 %).

^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.95 (s, 1H), 7.89 (t, *J* = 8.0 Hz, 4H), 7.62 (t, *J* = 8.1 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H).

Tert-butyl (*E*)-Benzylidenecarbamate (2f)[27]



2f

A flask was charged with anhydrous potassium carbonate (77.7 mmol, 10.7 g) and anhydrous sodium sulfate (91.5 mmol, 13.0 g). The solids were placed under vacuum and flame-dried. Then, *tert*-butyl phenyl(phenylsulfonyl)methylcarbamate (13.0 mmol, 4.50 g) was added and the flask purged with nitrogen. Dry THF (120 mL) was then added and the reaction refluxed overnight. After cooling to room temperature the solids were removed by filtration and the filtrate concentrated and dried in vacuo to give the product as colourless oil (2.56 g, 96%) with spectroscopic data in accordance to the literature.

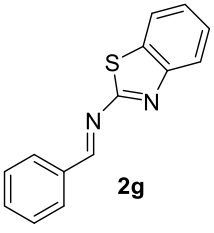
^{1}H NMR (400 MHz, $CDCl_3$): 8.88 (s, 1H), 7.93 – 7.91 (m, 2H), 7.59 – 7.55 (m, 1H), 7.49 – 7.46 (m, 2H), 1.59 (s, 9H).

[26] M. K. Ghorai, S. Das, K. Das, A. Kumara, *Org. Biomol. Chem*, **2015**, *13*, 9042.
[27] A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964.

4.6.2.1. General method for the synthesis of (*E*)-*N*-(benzo[*d*]thiazol-2-yl)-1-methanimine (2g-2v).

To a solution of the corresponding benzo[d]thiazol-2-amine (1.0 mmol, 1.0 eq.) in dry diethyl ether (0.5 M) were added the corresponding benzaldehyde (1.3 mmol, 1.43 eq.) and molecular sieves of 4 Å (800 mg/mmol). The mixture was stirred at room temperature overnight. After that time, the reaction mixture was filtrated through a pad of Celite and the filtrate was concentrated in vacuo.

(*E*)-*N*-(Benzo[*d*]thiazol-2-yl)-1-phenylmethanimine (2g)[28]

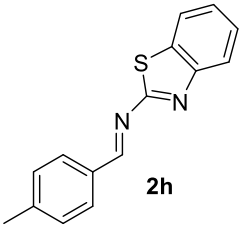


2g

It was prepared according to the general method. The product was obtained as a yellow solid, was used without further purification and with spectroscopic data in accordance to the literature. (Yield= 91 %).

^{1}H NMR (300 MHz, $CHCl_3$) δ 8.72 (s, 1H), 8.04 - 7.98 (m, 2H), 7.50 - 7.43 (m, 2H), 7.39 - 7.27 (m, 5H).

(*E*)-*N*-(Benzo[*d*]thiazol-2-yl)-1-(p-tolyl)methanimine (2h)



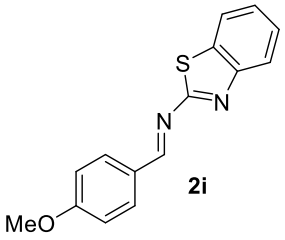
2h

It was prepared according to the general method. The product was obtained as a yellow solid and was used without further purification. (Yield= 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.94 – 7.81 (m, 3H), 7.74 (dd, *J* = 11.4, 4.2 Hz, 1H), 7.39 (ddd, *J* = 9.7, 3.0, 1.5 Hz, 1H), 7.33 – 7.16 (m, 3H), 2.37 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.0, 156.0, 153.5, 152.0, 144.3, 135.2, 130.3, 129.8, 126.4, 124.9, 123.0, 121.7, 21.8. **HRMS (ESI+):** calculated for $C_{15}H_{13}N_2S$ $(M+H)^+$: 253.0748; found: 253.0711.

[28] H. Xiao, W. Yang, D. Du, *Adv.Synth.Catal.* **2013**, *355*, 1137.

(*E*)-*N*-(Benzo[*d*]thiazol-2-yl)-1-(4-methoxyphenyl)methanimine (2i)

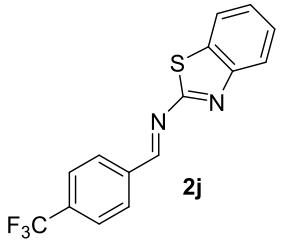


2i

It was prepared according to the general method. The product was obtained as a yellow solid and was used without further purification. (Yield= 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.92 (m, *J* = 8.8, 2.0 Hz, 2H), 7.77 (dd, *J* = 9.8, 4.9 Hz, 2H), 7.49 – 7.37 (m, 1H), 7.29 (dd, *J* = 10.8, 4.4 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.2, 150.7, 133.3, 131.2, 130.8, 126.8, 125.2, 123.4, 121.7, 120.5, 113.4, 112.9, 54.4. **HRMS (ESI+):** calculated for $C_{15}H_{12}N_2OSNa$ $(M+Na)^+$: 291.0551; found: 291.0522.

(*E*)-*N*-(Benzo[*d*]thiazol-2-yl)-1-(4-(trifluoromethyl)phenyl)methanimine (2j)

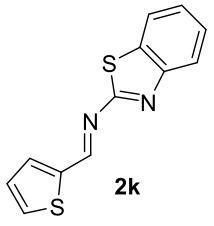


2j

It was prepared according to the general method. The product was obtained as a yellow solid and was used without further purification. (Yield= 84%).

^{1}H NMR (300 MHz, CD_2Cl_2) δ 9.09 (s, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.45 – 7.35 (m, 2H), 7.14 – 7.10 (m, 2H). **^{13}C NMR** (75 MHz, CD_2Cl_2): δ 163.1, 151.1, 150.6, 136.7 (q, J_{CF}= 29.8 Hz), 133.9 (q, J_{CF}= 3.7 Hz), 130.7, 129.2, 125.6 (q, J_{CF}= 4.7 Hz), 124.3 (q, J_{CF}= 262.1 Hz), 122.3, 121.3, 119.9, 118.4. **HRMS (ESI+):** calculated for $C_{15}H_{10}F_3N_2S$ $(M+H)^+$: 307.0412; found: 307.0450.

(*E*)-*N*-(Benzo[*d*]thiazol-2-yl)-1-(thiophen-2-yl)methanimine (2k)



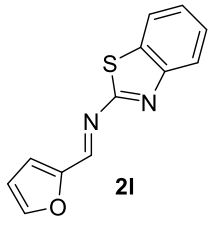
2k

It was prepared according to the general method. The product was obtained as a yellow solid and was used without further purification. (Yield= 93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.64 - 7.56 (m, 2H), 7.42 - 7.33 (m,

1H), 7.30 - 7.22 (m, 1H), 7.10 (dd, *J* = 4.9, 3.8 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.4, 158.0, 151.7, 141.3, 135.9, 134.8, 133.9, 128.5, 126.4, 124.9, 122.9, 121.7. **HRMS (ESI+):** calculated for $C_{12}H_8N_2S_2Na$ $(M+Na)^+$: 266.9904; found: 266.9922.

(*E*)-*N*-(Benzo[*d*]thiazol-2-yl)-1-(furan-2-yl)methanimine (2l)[28]

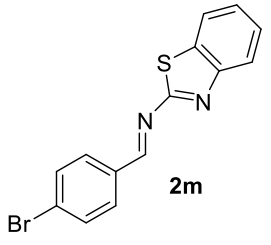


2l

It was prepared according to the general method. The product was obtained as a yellow solid, was used without further purification and with spectroscopic data in accordance to the literature. (Yield= 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.09 - 8.01 (m, 2H), 7.92 - 7.86 (m, 2H), 7.56 - 7.44 (m, 1H), 6.85 (d, *J* = 4.4 Hz, 1H), 6.51 (t, *J* = 7.5 Hz, 1H).

(*E*)-*N*-(Benzo[*d*]thiazol-2-yl)-1-(4-bromophenyl)methanimine (2m)[28]

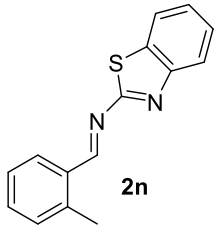


2m

It was prepared according to the general method. The product was obtained as a yellow solid, was used without further purification and with spectroscopic data in accordance to the literature. (Yield= 97%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.06 – 7.89 (m, 2H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.49 – 7.41 (m, 2H), 7.26 (d, *J* = 7.5 Hz, 2H).

(*E*)-N-(Benzo[*d*]thiazol-2-yl)-1-(o-tolyl)methanimine (2n)

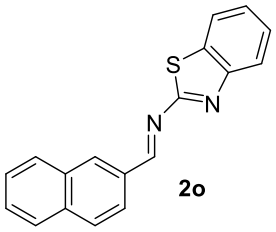


2n

It was prepared according to the general method. The product was obtained as a yellow solid and was used without further purification. (Yield= 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.46 - 7.31 (m, 2H), 7.30 - 7.11 (m, 3H), 2.60 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.3, 164.8, 151.8, 140.7, 134.7, 132.9, 132.7, 131.3, 129.4, 126.5, 126.4, 124.9, 123.0, 121.7, 19.7. **HRMS (ESI+):** calculated for $C_{15}H_{12}N_2SNa$ $(M+Na)^+$: 275.0518; found: 275.0517.

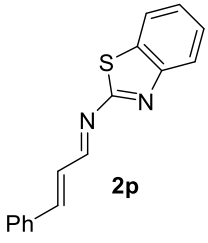
(*E*)-*N*-(Benzo[*d*]thiazol-2-yl)-1-(naphthalen-2-yl)methanimine (2o)



It was prepared according to the general method. The product was obtained as a yellow solid and was used without further purification. (Yield= 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.31 (s, 1H), 8.18 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.97 – 7.76 (m, 5H), 7.58 – 7.47 (m, 2H), 7.46 – 7.38 (m, 1H), 7.35 – 7.27 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.8, 166.1, 165.6, 151.8, 135.9, 134.0, 132.9, 132.5, 129.2, 129.0, 128.6, 128.0, 126.9, 126.5, 125.1, 124.1, 123.1, 121.7. **HRMS (ESI+):** calculated for $C_{18}H_{12}N_2SNa$ $(M+Na)^+$: 311.0544; found: 311.0528.

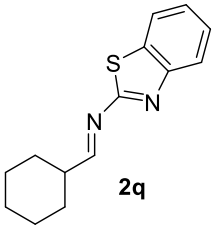
(1*E*,2*E*)-*N*-(Benzo[*d*]thiazol-2-yl)-3-phenylprop-2-en-1-imine (2p)



It was prepared according to the general method. The product was obtained as a yellow solid and was used without further purification. (Yield= 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (d, *J* = 9.1 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.81 (dd, *J* = 7.9, 0.6 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.51 – 7.30 (m, 6H), 7.16 (dd, *J* = 15.9, 9.1 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.8, 167.0, 151.8, 149.2, 135.0, 134.8, 130.6, 129.0, 128.1, 127.4, 126.4, 124.9, 123.0, 121.7. **HRMS (ESI+):** calculated for $C_{16}H_{12}N_2SNa$ $(M+Na)^+$: 287.0522 found: 287.0538.

(*E*)-*N*-(Benzo[*d*]thiazol-2-yl)-1-cyclohexylmethanimine (2q)

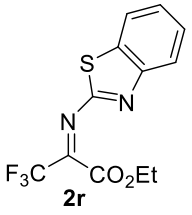


It was prepared as follows: To a solution of benzo[d]thiazol-2-amine (1.0 mmol, 1.0 eq.) in DCM (0.5 M) were added ciclohexenecarbaldehyde (1.0 mmol, 1eq.) and 4 eq. of $Ti(OEt)_4$ .The mixture was heated at reflux for 12 hours. After that time, $NaHCO_3$ is added and the product was obtained as a yellow solid after filtration through a pad of Celite (64% yield).

^{1}H NMR (300 MHz, $CDCl_3$) 8.43 (d, *J* = 7.0 Hz, 1H), 7.50 (dd, *J* = 7.6, 1.5 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 2.27 – 2.09 (m, 1H), 1.93 – 1.75 (m,

2H), 1.74 – 1.60 (m, 3H), 1.41 – 1.12 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 160.0, 155.7, 151.9, 135.1, 125.0, 123.10, 121.9, 119.1, 49.7, 25.84, 25.82, 24.8. **HRMS (ESI+):** calculated for $C_{14}H_{16}N_2SNa$ $(M+Na)^+$: 267.0998; found: 267.0974.

Ethyl 2-(Benzo[*d*]thiazol-2-ylimino)-3,3,3-trifluoropropanoate (2r)[29]

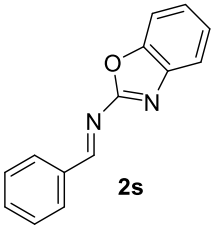


2r

Methyl trifluoropyruvate (20 mmol) was added dropwise to a stirred suspension of benzo[d]thiazol-2-amine (20 mmol) in toluene at r.t. The reaction is spountaneously warmed and became homogeneous. The mixture was left for 1 hour at r.t. and then thionyl chloride (20 mmol) was added. After 15 min pyridine (40 mmol) was added dropwise to stirred and cooled to 0ºC mixture and allowed to warm to r.t. Pyridine hydrochloride was filtered off, the solvent evaporated under reduced pressure to give iminotrifluoropropanoate **2r** as a white solid. The crude was used without further purification. (Yield= 75%).

^{1}H NMR (300 MHz, CDCl3) 7.50 (dd, *J* = 9.8, 4.9 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 4.45 (q, *J* = 7.4 Hz, 2H), 1.26 (t, *J* = 7.4 Hz, 3H).

(*E*)-*N*-(Benzo[*d*]oxazol-2-yl)-1-phenylmethanimine (2s)



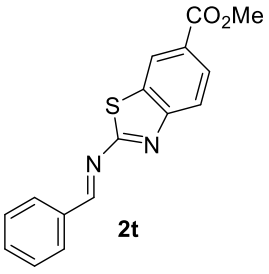
2s

It was prepared according to the general method. The product was obtained as a yellow solid and was used without further purification. (Yield= 76%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 2H), 7.65 (dd, *J* = 6.5, 2.6 Hz, 1H), 7.59 - 7.41 (m, 4H), 7.33 - 7.23 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.3, 163.2, 149.0, 140.8, 133.7, 132.8, 129.4, 128.0, 124.0, 123.6, 118.9, 109.5. **HRMS (ESI+):** calculated for $C_{14}H_{10}N_2ONa$ $(M+Na)^+$: 245.0677; found: 245.0695.

[29] Y.V. Rassukana, *J. Fluorine Chem.*, **2013**, *148*, 14.

Methyl (*E*)-2-(Benzylideneamino)benzo[*d*]thiazole-6-carboxylate (2t)

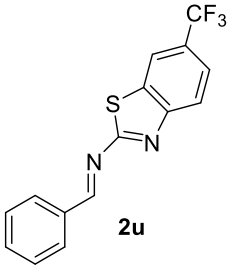


2t

It was prepared according to the general method. The product was obtained as a yellow solid and was used without further purification. (Yield= 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.49 (s, 1H), 8.16 - 8.02 (m, 1H), 8.03 - 7.84 (m, 3H), 7.54 -7.49 (m, 3H), 3.89 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.8, 166.1, 165.5, 153.8, 133.5, 132.6, 129.4, 128.0, 126.6, 122.8, 121.9, 121.6, 118.3, 51.3. **HRMS (ESI+):** calculated for $C_{16}H_{13}N_2O2S$ $(M+H)^+$: 297.0623; found: 297.0655.

(*E*)-1-Phenyl-*N*-(6-(trifluoromethyl)benzo[*d*]thiazol-2-yl)methanimine (2u)

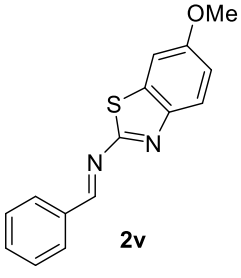


2u

It was prepared according to the general method. The product was obtained as a yellow solid and was used without further purification. (Yield= 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.05 (s, 1H), 7.97 (d, *J* = 6.7 Hz, 3H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.49 (dq, *J* = 14.5, 7.2 Hz, 3H**). ^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.4, 166.2, 152.8, 133.8, 133.4, 132.7, 129.4, 126.1(dq, J_{CF}=212 Hz), 125.2 (dq, J_{CF}= 33.3 Hz), 122.4, 122.3 (dq, J_{CF}= 7.1 Hz), 122.2, 118.3 (dq, J_{CF}= 4.3 Hz). **HRMS (ESI+):** calculated for $C_{15}H_9N_2F_3SNa$ (M+Na)+: 329.0241; found: 329.0214.

***N*-(6-Methoxybenzo[*d*]thiazol-2-yl)-1-phenylmethanimine (2v)[28]**

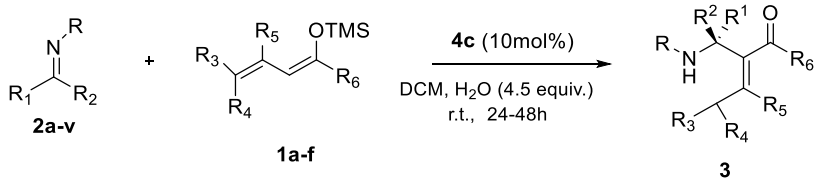


2v

It was prepared according to the general method. The product was obtained as a yellow solid, was used without further purification and with spectroscopic data in accordance to the literature . (Yield= 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.98 (d, *J* = 7.3 Hz, 1H), 7.74 (d, *J* = 1.6 Hz, 1H), 7.35 - 7.29 (m, 3H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.02 - 6.94 (m, 2H), 3.83 (s, 3H).

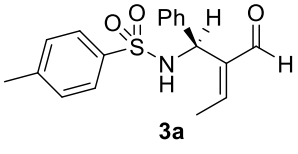
4.6.3. General Procedure for the synthesis of Baylis-Hillman Products 3 and characterization data.



Scheme 19.

The corresponding imine **2a-2v** (0.1 mmol, 1.0 eq.) and 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1*R*,2*R*)-2-(dimethylamino)ciclohexyl)thiourea (10 mol %) **4c** were dissolved in 0.3 ml of dichloromethane. Then, 3 equiv. of the corresponding silyl-dienolether **1a-f** and 10 µl of water were added to the previous solution. The resulting mixture was stirred at room temperature. Upon completion (24-48 h determined by TLC), the solvent was removed under reduced pressure. The residue was purified by flash column chromatography. In all cases the enantiomeric excesses were determined without any further derivatization.

(*S, E*)-*N*-(2-Formyl-1-phenylbut-2-en-1-yl)-4-methylbenzenesulfonamide (3a)

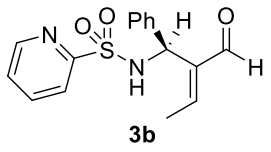


Following the general procedure described above, compound **3a** was obtained in 78% yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.23 – 7.09 (m, 7H), 6.48 (q, *J* = 7.1 Hz, 1H), 6.28 (d, *J* = 10.2 Hz, 1H), 5.45 (d, *J* = 10.2 Hz, 1H), 2.32 (s, 3H), 1.94 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 193.5, 151.3, 142.2, 140.6, 137.2, 137.0, 128.3, 127.5, 126.5, 126.0, 125.1, 52.3, 20.4, 14.1. **HRMS (ESI+):** calculated for $C_{18}H_{19}NO_3SNa$ $(M+Na)^+$: 352.0962; found: 352.0977. $[\alpha]_D^{20}$= -14.13 (c = 0.3, $CHCl_3$). The enantiomeric excess was determined by SFC using

Chiralpak IB column [CO_2/MeOH (95:5), 120 bar, 40 ºC, 3.0 mL/min]: τ_{major} = 6.62 min, τ_{minor} = 7.16 min (50 % ee).

(*S, E*)-N-(2-Formyl-1-phenylbut-2-en-1-yl)pyridine-2-sulfonamide (3b)

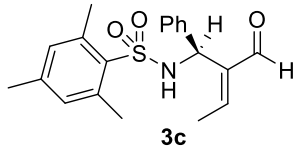


3b

Following the general procedure described above, compound **3b** was obtained in 65% yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.51 (dd, *J* = 3.1, 0.9 Hz, 1H), 7.98 – 7.59 (m, 2H), 7.32 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 1H), 7.22 – 7.02 (m, 5H), 6.63 (d, *J* = 9.9 Hz, 1H), 6.52 (q, *J* = 7.1 Hz, 1H), 5.66 (d, *J* = 9.9 Hz, 1H), 2.00 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 193.2, 157.2, 150.8, 148.7, 141.1, 137.3, 136.5, 127.4, 126.5, 125.3, 125.2, 120.5, 52.9, 14.1. **HRMS (ESI+):** calculated for $C_{16}H_{17}N_2O_3S$ $(M+H)^+$: 317.0949; found: 317.0954. $[\alpha]_D^{20}$= -10.92 (c = 0.5, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IB column [CO_2/MeOH (95:5), 120 bar, 40 ºC, 3.0 mL/min]: τ_{major} = 9.61 min, τ_{minor} = 9.94 min (53% ee).

(*S, E*)-*N*-(2-Formyl-1-phenylbut-2-en-1-yl)-2,4,6-trimethylbenzenesulfonamide (3c)



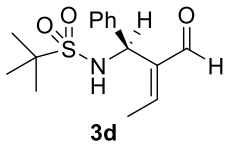
3c

Following the general procedure described above, compound **3c** was obtained in 83% yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.17 - 7.11 (m, 5H), 6.80 (s, 2H), 6.53 (q, *J* = 7.1 Hz, 1H), 6.35 (d, *J* = 10.1 Hz, 1H), 5.42 (d, *J* = 10.0 Hz, 1H), 2.51 (s, 6H), 2.19 (s, 3H), 1.89 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.6, 152.1, 141.9, 141.7, 138.7, 138.4, 134.8, 131.8, 128.5, 127.5, 126.1, 53.0, 22.9, 20.8, 15.0. **HRMS (ESI+):** calculated for $C_{20}H_{24}NO_3S$ (M+): 358.1470; found: 358.1471. $[\alpha]_D^{20}$= -15.03 (c = 0.55, $CHCl_3$). The enantiomeric excess was determined by SFC

using Chiralpak IB column [CO_2/MeOH (95:5), 120 bar, 40 ºC, 3.0 mL/min]: τ_{minor} = 6.19 min, τ_{major} = 6.42 min (53% *ee*).

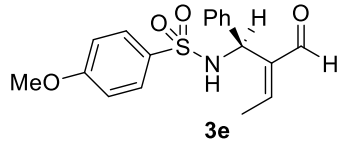
(*S, E*)-N-(2-Formyl-1-phenylbut-2-en-1-yl)-2-methylpropane-2-sulfonamide (3d)



Following the general procedure described above, compound **3d** was obtained in 78% yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.35 – 7.13 (m, 5H), 6.74 (q, *J* = 7.1 Hz, 1H), 5.73 (d, *J* = 10.0 Hz, 1H), 5.53 (d, *J* = 10.0 Hz, 1H), 2.13 (d, *J* = 7.1 Hz, 3H), 1.29 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.9, 151.7, 143.3, 139.5, 128.6, 127.5, 126.0, 59.8, 54.1, 24.1, 15.1. **HRMS (ESI+)**: calculated for $C_{15}H_{22}NO_3S$ $(M+H)^+$: 296.1307; found: 296.1314. $[\alpha]_D^{20}$= -12.16 (c = 0.65, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IB column [CO_2/MeOH (95:15), 120 bar, 40 ºC, 3.0 mL/min]: τ_{major} = 2.59 min, τ_{minor} = 2.70 min (10% *ee*).

(*S, E*)-N-(2-Formyl-1-phenylbut-2-en-1-yl)-4-methoxybenzenesulfonamide (3e)

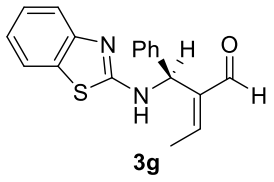


Following the general procedure described above, compound **3e** was obtained in 81% yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.76 – 7.45 (m, 2H), 7.35 – 7.01 (m, 5H), 6.80 (d, *J* = 9.0 Hz, 2H), 6.50 (q, *J* = 7.1 Hz, 1H), 6.28 (d, *J* = 10.2 Hz, 1H), 5.45 (d, *J* = 10.2 Hz, 1H), 3.77 (s, 3H), 1.95 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.6, 162.7, 152.4, 141.7, 138.2, 136.8, 132.7, 131.2, 129.1, 128.5, 127.6, 126.1, 113.9, 55.6, 53.3, 15.1. **HRMS (ESI+):** calculated for $C_{18}H_{20}NO_4S$ (M+H)+: 346.1107, found: 346.1118. $[\alpha]_D^{20}$= -14.01 (c = 0.6, $CHCl_3$). The enantiomeric excess

was determined by SFC using Chiralpak IB column [CO_2/MeOH (95:5), 120 bar, 40ºC, 3.0 mL/min]: τ_{major} = 9.06 min, τ_{minor} = 9.60 min (48% *ee*).

(*S, E*)-2-((Benzo[*d*]thiazol-2-ylamino)(phenyl)methyl)but-2-enal (3g)

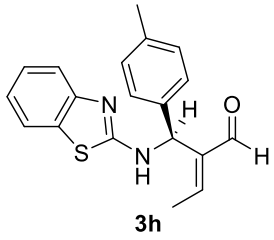


3g

Following the general procedure described above, compound **3g** was obtained in 84% yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.55 (m, 2H), 7.43 - 7.22 (m, 6H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.88 (q, *J* = 7.1 Hz, 1H), 6.73 (brs, 1H), 6.31 (brd, 1H), 2.29 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.0, 166.0, 152.8, 152.4, 142.5, 139.3, 130.8, 128.6, 127.5, 126.16, 125.8, 121.8, 120.8, 119.3, 54.4, 15.5. **HRMS (ESI+):** calculated for $C_{18}H_{16}N_2OSNa$ $(M+Na)^+$: 331.0876; found: 331.0892. $[\alpha]_D^{20}$ = -67.4 (c = 0.74, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IB-3 column [CO_2/MeOH (90:10), 120 bar, 40 ºC, 3.0 mL/min]: τ_{major} = 5.59 min, τ_{minor} = 5.98min (>99% *ee*).

(*S, E*)-2-((Benzo[*d*]thiazol-2-ylamino)(p-tolyl)methyl)but-2-enal (3h)

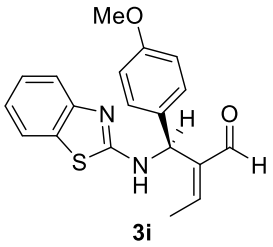


3h

Following the general procedure described above, compound **3h** was obtained in 87% yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.47 (m, 2H), 7.20 (m, 3H), 7.11 – 6.95 (m, 3H), 6.78 (q, *J* = 7.1 Hz, 1H), 6.66 (brs, 1H), 6.17 (brs, 1H), 2.24 (s, 3H), 2.20 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.1, 165.5, 152.8, 152.4, 142.6, 137.3, 136.3, 130.7, 129.4, 126.1, 125.8, 121.8, 120.8, 119.2, 55.4, 21.0 15.5. **HRMS (ESI+):** calculated for $C_{19}H_{18}N_2OSNa$ $(M+Na)^+$: 345.0952; found: 345.0977. $[\alpha]_D^{20}$= -57.7 (c = 0.82, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IG-3 column [CO_2/MeOH (85:15), 120 bar, 40 ºC, 3.0 mL/min]: τ_{major} = 24.24 min, τ_{minor} = 26.31 min(>99% *ee*).

(*S, E*)-2-((Benzo[*d*]thiazol-2-ylamino)(4-methoxyphenyl)methyl)but-2-enal (3i)

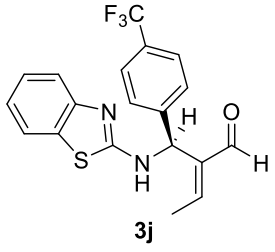


3i

Following the general procedure described above, compound **3i** was obtained in 80 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.53 - 7.47 (m, 2H), 7.30 – 7.12 (m, 3H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.77 (m, 3H), 6.64 (bs, 1H), 6.14 (bs, 1H), 3.70 (s, 3H), 2.19 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.1, 165.0, 158.0, 151.7, 151.4, 141.6, 130.4, 126.4, 124.8, 120.7, 119.7, 118.2, 113.0, 54.3, 53.1, 14.4. **HRMS (ESI+):** calculated for $C_{19}H_{18}N_2O_2SNa$ $(M+Na)^+$: 361.0991; found: 361.0975. $[\alpha]_D^{20}$ = -64.3 (c = 0.80, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IG-3 column [CO_2/MeOH (85:15), 120 bar, 40 ºC, 3.0 mL/min]: τ_{major} = 26.30 min, τ_{minor} = 27.65 min (>99% *ee*).

(*S, E*)-2-((Benzo[*d*]thiazol-2-ylamino)(4-(trifluoromethyl)phenyl)methyl)but-2-enal (3j)



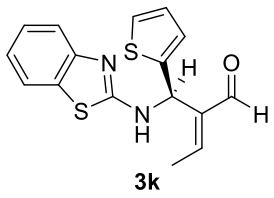
3j

Following the general procedure described above, compound **3j** was obtained in 75 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.56 – 7.47 (m, 3H), 7.47 – 7.39 (m, 2H), 7.28 – 7.21 (m, 2H), 7.08 – 6.98 (m, 1H), 6.86 (q, *J* = 7.4 Hz, 1H), 6.77 (m, 1H), 6.35 (brs, 1H), 2.25 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 192.3, 156.9, 151.7, 146.6, 144.2, 135.9, 135.0, 131.2 (q, J_{CF} = 3.6 Hz), 130.9 (q, J_{CF} = 30.2 Hz), 125.5 , 124.8 (q, J_{CF} = 7.6 Hz) , 124.0 (q, J_{CF} = 270.1 Hz), 122.8, 121.3, 118.7, 57.8, 14.5. **HRMS (ESI+):** calculated for $C_{19}H_{16}F_3N_2OS$ $(M+H)^+$: 377.0815; found: 377.0825. $[\alpha]_D^{20}$ = -52.3 (c = 0.58, $CHCl_3$). The

enantiomeric excess was determined by SFC using Chiralpak IG-3 column [CO_2/MeOH (85:15), 120 bar, 40 ºC, 3.0 mL/min]: τ_{major}= 5.65 min, τ_{minor} = 6.38min (>99 *ee*).

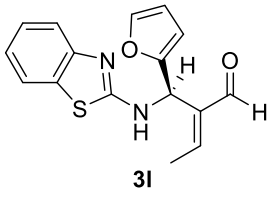
(*S*, *E*)-2-((Benzo[*d*]thiazol-2-ylamino)(thiophen-2-yl)methyl)but-2-enal (3k)



Following the general procedure described above, compound **3k** was obtained in 78 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (s, 1H), 7.50 (m, 2H), 7.27 – 7.18 (m, 1H), 7.13 (dd, *J* = 4.7, 1.6 Hz, 1H), 7.08 – 6.98 (m, 1H), 6.90 – 6.83 (m, 2H), 6.79 (q, *J* = 7.1 Hz, 1H), 6.69 (bs, 1H), 6.45 (bs, 1H), 2.21 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 193.7, 164.4, 151.8, 151.2, 142.2, 141.0, 129.9, 125.9, 124.8, 123.9, 123.6, 120.9, 119.8, 118.4, 50.0, 14.2. **HRMS (ESI+):** calculated for $C_{16}H_{14}N_2OS_2Na$ $(M+Na)^+$: 337.0344; found: 337.0325. $[\alpha]_D^{20}$ = -44.4 (c = 0.74, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IG-3 column [CO_2/MeOH (85:15), 120 bar, 40 ºC, 3.0 mL/min]: τ_{major}= 12.79 min, τ_{minor} = 17.47min (>99 % *ee*).

(*S*, *E*)-2-((Benzo[*d*]thiazol-2-ylamino)(furan-2-yl)methyl)but-2-enal (3l)

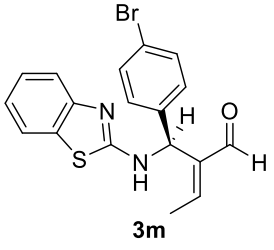


Following the general procedure described above, compound **3l** was obtained in 82 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.36 (d, *J* = 9.3 Hz, 1H), 7.30 – 7.10 (m, 2H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.85 (q, *J* = 7.9 Hz, 1H), 6.46 (d, *J* = 3.2 Hz, 1H), 6.35 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.05 (d, *J* = 3.9 Hz, 1H), 4.65 (dd, *J* = 13.8, 7.1 Hz, 1H), 3.01 (d, *J* = 4.1 Hz, 1H), 1.53 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.3, 158.4, 152.9, 141.0, 138.6, 125.0, 121.7, 121.3, 121.0, 109.6, 107.1, 106.8,

50.1, 49.1, 46.3, 18.9. **HRMS (ESI+):** calculated for $C_{16}H_{15}N_2O2S$ $(M+H)^+$: 299.0855; found: 299.0823. $[\alpha]_D^{20}$ = -31.2 (c = 0.5, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IG-3 column [CO_2/MeOH (85:15), 120 bar, 40 ºC, 3.0 mL/min]: τ_{major}= 7.58 min, τ_{minor}= 9.55 min (94% *ee*).

(*S, E*)-2-((Benzo[*d*]thiazol-2-ylamino)(4-bromophenyl)methyl)but-2-enal (3m)

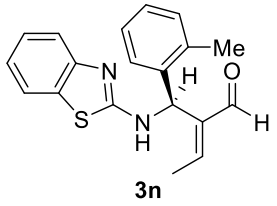


3m

Following the general procedure described above, compound **3m** was obtained in 86 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39 (s, 1H), 7.60 - 7.54 (m, 2H), 7.47 – 7.38 (m, 2H), 7.32 – 7.19 (m, 3H), 7.14 – 7.04 (m, 1H), 6.88 (q, *J* = 7.1 Hz, 1H), 6.72 (brs, 1H), 6.29 (brs, 1H), 2.28 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 193.9, 164.7, 152.1, 151.2, 141.1, 137.5, 130.8, 130.7, 129.8, 126.9, 124.8, 120.9, 119.8, 118.3, 52.7, 14.5. **HRMS (ESI+):** calculated for $C_{18}H_{15}N_2OBrSNa$ $(M+Na)^+$: 408.9974; found: 408.9953. $[\alpha]_D^{20}$ = -50.1 (c = 0.62, $CHCl_3$).The enantiomeric excess was determined by SFC using Chiralpak IB column [CO_2/MeOH (90:10), 120 bar, 40 ºC, 3.0 mL/min]: τ_{major}= 9.20 min, τ_{minor} = 10.04min (>99% *ee*).

(*S, E*)-2-((Benzo[*d*]thiazol-2-ylamino)(o-tolyl)methyl)but-2-enal (3n)



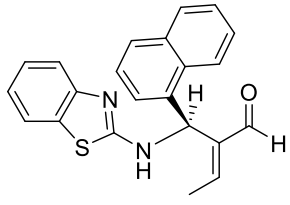
3n

Following the general procedure described above, compound **3n** was obtained in 81 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.53 - 7.47 (m, 2H), 7.28 – 7.09 (m, 5H), 7.04 – 6.96 (m, 1H), 6.78 (q, *J* = 7.2 Hz, 1H), 6.23 (s, 1H), 2.37 (s, 3H), 2.10 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.0, 165.5, 159.0, 153.3, 142.0, 136.7,

136.6, 130.9, 128.0, 127.0, 126.1, 125.7, 121.7, 120.7, 119.3, 108.1, 52.8, 19.7, 15.5. **HRMS (ESI+):** calculated for $C_{19}H_{19}N_2OS$ $(M+H)^+$: 323.1102; found: 323.1125. $[\alpha]_D^{20}$ = -40.7 (c = 0.65, $CHCl_3$).The enantiomeric excess was determined by SFC using Chiralpak IG-3 column [CO_2/MeOH (85:15),120 bar, 40 ºC, 3.0 mL/min]: τ_{major}= 8.00 min, τ_{minor} = 10.43 min (99% *ee*).

(*S*, *E*)-2-((Benzo[*d*]thiazol-2-ylamino)(naphthalen-1-yl)methyl)but-2-enal (3o)

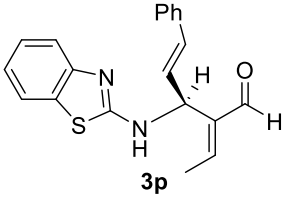


3o

Following the general procedure described above, compound **3o** was obtained in 83% yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39 (s, 1H), 7.77 – 7.68 (m, 3H), 7.53 – 7.35 (m, 4H), 7.25 – 7.17 (m, 3H), 7.06 – 6.97 (m, 1H), 6.85 (q, *J* = 7.1 Hz, 1H), 6.76 (brd, 1H), 6.40 (brd, 1H), 2.26 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.0, 165.0, 152.0, 151.4, 141.4, 135.7, 132.2, 131.7, 129.8, 127.5, 127.0, 126.5, 125.2, 125.0, 124.8, 123.8, 123.3, 120.8, 119.7, 118.3, 53.6, 14.5**. HRMS (ESI+):** calculated for $C_{22}H_{19}N_2OS$ $(M+H)^+$: 359.1142; found: 359.1126. $[\alpha]_D^{20}$= -65.9 (c = 0.75, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IB-3 column [CO_2/MeOH (80:20), 120 bar, 40 ºC, 2.0 mL/min]: τ_{major}= 2.89 min, τ_{minor} = 4.75 min (>99 % ee).

(*S*, 2*E*, 4*E*)-3-(Benzo[*d*]thiazol-2-ylamino)-2-ethylidene-5-phenylpent-4-enal (3p)

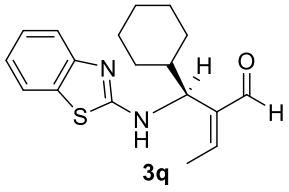


3p

Following the general procedure described above, compound **3p** was obtained in 75 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.55 - 7.49 (m, 2H), 7.32 – 7.14 (m, 7H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.74 (q, *J* = 7.1 Hz, 1H), 6.53 (d, *J* = 15.6 Hz, 1H), 6.28 (dd, *J* = 15.6, 6.2 Hz, 1H), 5.74 (brs, 1H), 2.20 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 193.9, 157.2, 151.5, 147.3, 130.6, 130.2, 127.5, 126.9, 125.5, 124.8, 122.5, 121.7, 120.7, 119.7, 118.2, 117.7, 52.3, 14.3. **HRMS (ESI+):** calculated for $C_{20}H_{18}N_2OSNa$ $(M+Na)^+$: 357.0988; found: 357.0977. $[\alpha]_D^{20}$= -32.1 (c =0.64, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IB-3 column [CO_2/MeOH (80:20), 120 bar, 40 ºC, 2.0 mL/min]: τ_{major}= 7.09 min, τ_{minor}= 7.83 min (93 % *ee*).

(*S*, *E*)-2-((Benzo[*d*]thiazol-2-ylamino)(cyclohexyl)methyl)but-2-enal (3q)

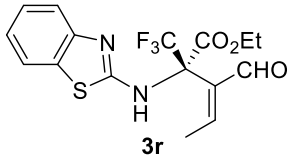


3q

Following the general procedure described above, compound **3q** was obtained in 62 % yield as a yellow oil after 72 h of reaction. (93:7 diasteromeric ratio). The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR Major diasteroisomer (300 MHz, $CDCl_3$) 9.70 (s, 1H), 7.70 - 7.64 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.72 (q, *J* = 7.9 Hz, 1H), 6.12 (bs, 1H), 3.40 (m, 1H), 2.11 (d, *J* = 7.1 Hz, 3H), 1.76 – 1.65 (m, 2H), 1.63 – 1.48 (m, 3H), 1.32-1.05 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 192.3, 158.1, 152.4, 149.3, 145.1, 134.1, 126.0, 122.6, 121.3, 119.7, 58.1, 42.0, 28.1, 25.8, 25.6, 14.7. **HRMS (ESI+):** calculated for $C_{18}H_{23}N_2OS$ $(M+H)^+$: 315.1512; found: 315.1538. $[\alpha]_D^{20}$= -47.20 (c =0.42, $CHCl_3$).The enantiomeric excess was determined by SFC using Chiralpak IG-3 column [CO_2/MeOH (85:15), 120 bar, 40 ºC, 3.0 mL/min]: τ_{major}= 11.98 min, τ_{minor}=14.64 min (86 % *ee*).

Ethyl (*R*, *E*)-2-(benzo[*d*]thiazol-2-ylamino)-3-formyl-2-phenylpent-3-enoate (3r)



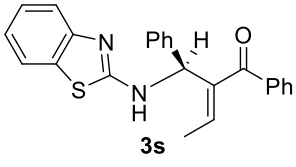
3r

Following the general procedure described above, compound **3r** was obtained in 69 % yield as a yellow oil after 48 h of reaction. The crude product was purified by

flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.61 - 7.55 (m, 2H), 7.33 – 7.22 (m, 2H), 6.57 (q, *J* = 6.7 Hz, 1H), 5.82 (bs, 1H), 4.21 (q, *J* = 5.9 Hz, 2H), 2.03 (d, *J* = 6.7 Hz, 3H), 1.40 (t, *J* = 5.9 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 191.1, 167.0 (q, J_{CF} = 25.7 Hz), 162.2, 154.7, 151.8, 143.9, 135.0, 125.5, 122.9, 121.2, 119.4 (q, J_{CF} = 277.4 Hz), 118.4, 76.3, 62.6, 14.7, 13.5. **HRMS (ESI+):** calculated for $C_{16}H_{15}F_3N_2O_3SNa$ $(M+Na)^+$: 395.0798; found: 395.0772. $[\alpha]_D^{20}$ = +51.3 (c =0.5, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IG-3 column [CO_2/MeOH (80:20), 120 bar, 40 ºC, 2.0 mL/min]: τ_{minor}= 8.07 min, τ_{major}= 11.00 min (87 % *ee*).

(*S*, *E*)-2-((Benzo[*d*]thiazol-2-ylamino)(phenyl)methyl)-1-phenylbut-2-en-1-one (3s)

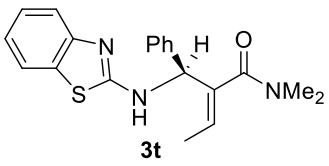


3s

Following the general procedure described above, compound **3s** was obtained in 75 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 3H), 7.58 – 7.30 (m, 3H), 7.27 – 7.13 (m, 4H), 7.01 (m, 3H), 6.89 – 6.78 (m, 2H), 6.76 (brs, 1H), 6.55 (q, *J* = 7.0 Hz, 1H), 6.42 (brs, 1H), 2.12 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 191.1, 157.0, 151.7, 139.6, 138.2, 135.6, 133.1, 132.5, 129.5, 128.7, 128.6, 128.5, 128.2, 128.1, 125.7, 122.9, 121.5, 118.9, 53.1, 15.4. **HRMS (ESI+):** calculated for $C_{24}H_{21}N_2OS$ $(M+H)^+$: 385.1322; found: 385.1343. $[\alpha]_D^{20}$= -47.80 (c= 0.74, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IB-3 column [CO_2/MeOH (97:3), 120 bar, 40 ºC, 1.0 mL/min]: τ_{major}= 2.86 min, τ_{minor}= 3.14 min (98 % *ee*).

(*S*, *E*)-2-((Benzo[*d*]thiazol-2-ylamino)(phenyl)methyl)-N,N-dimethylbut-2-enamide (3t)

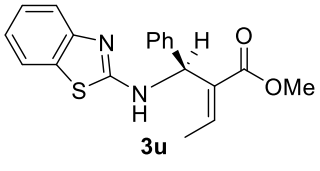


3t

Following the general procedure described above, compound **3t** was obtained in 76% yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 - 7.48 (m, 2H), 7.28 – 7.17 (m, 6H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.29 (q, *J* = 6.5 Hz, 1H), 6.13 (brs, 1H), 5.11 (brs, 1H), 2.98 (s, 6H), 1.91 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.5, 157.0, 152.7, 140.5, 134.9, 133.6, 131.1, 128.8, 128.5, 128.0, 125.6, 122.7, 121.3, 118.7, 57.5, 36.4, 15.3. **HRMS (ESI+):** calculated for $C_{20}H_{21}N_3OSNa$ $(M+Na)^+$: 374.1227; found: 374.1235. $[\alpha]_D^{20}$= +52.7 (c=0.5, $CHCl_3$) The enantiomeric excess was determined by SFC using Chiralpak-IG-3 column [CO_2/MeOH (85:15), 120 bar, 40 ºC, 3.0 mL/min]: τ_{minor}= 10.7 min, τ_{major}= 26.17 min (93 % *ee*).

Methyl (*S*, *E*)-2-((benzo[*d*]thiazol-2-ylamino)(phenyl)methyl)but-2-enoate (3u)

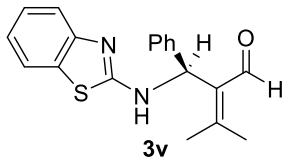


3u

Following the general procedure described above, compound **3u** was obtained in 79 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 - 7.50 (m, 2H), 7.40 – 7.20 (m, 6H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.43 (q, *J* = 7.1 Hz, 1H), 6.23 (brs, 1H), 4.80 (brs, 1H), 3.74 (s, 3H), 2.23 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 168.4, 157.1, 151.9, 139.5, 139.3, 135.1, 132.8, 129.1, 128.3, 128.1, 125.6, 122.9, 121.4, 118.2, 58.7, 52.0, 15.5. **HRMS (ESI+):** calculated for $C_{19}H_{18}N_2O2S$ $(M+H)^+$: 339.1198; found: 339.1173. $[\alpha]_D^{20}$= -35.2 (c= 0.52, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IG-3 column [CO_2/MeOH (80:20), 120 bar, 40 ºC, 2.0 mL/min]: τ_{major}= 6.47 min, τ_{minor}= 7.66 min (93 % *ee*).

(*S*)-2-((Benzo[*d*]thiazol-2-ylamino)(phenyl)methyl)-3-methylbut-2-enal (3v)

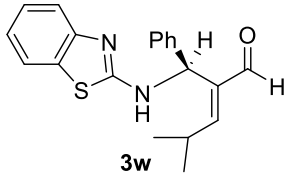


3v

Following the general procedure described above, compound **3v** was obtained in 87 % yield as a yellow oil after 72 h of reaction at 0ºC. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.55 - 7.46 (m, 2H), 7.34 – 7.10 (m, 6H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.67 (brd, 1H), 6.29 (brd, 1H), 2.26 (s, 3H), 2.25 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 190.4, 165.3, 158.0, 151.5, 139.0, 134.8, 129.7, 127.5, 126.1, 124.9, 124.7, 120.6, 119.7, 118.1, 55.0, 23.0, 19.4. HRMS (ESI+): calculated for $C_{19}H_{18}N_2OSNa$ $(M+Na)^+$: 345.0978; found: 345.0966. $[\alpha]_D^{20}$= -40.2, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IG-3 column [CO_2/MeOH (80:20), 120 bar, 40 ºC, 2.0 mL/min]: τ_{major}= 6.06 min, τ_{minor}= 6.60 min (92 % *ee*).

(*S, E*)-2-((Benzo[*d*]thiazol-2-ylamino)(phenyl)methyl)-4-methylpent-2-enal (3w)



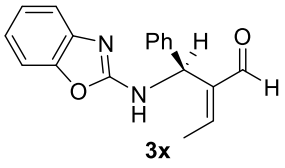
3w

Following the general procedure described above, compound **3w** was obtained in 70 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.54 - 7.48 (m, 2H), 7.36 – 7.18 (m, 6H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.70 (bs, 1H), 6.48 (d, *J* = 7.1 Hz, 1H), 6.25 (brd, 1H), 1.64 (m, 1H), 1.16 (d, *J* = 7.6 Hz, 3H), 0.87 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 191.3, 166.8, 156.7, 151.9, 139.2, 137.3, 135.6, 128.5, 127.9, 127.7, 125.6, 122.9, 121.5, 118.9, 59.4, 27.8, 22.7, 21.5. **HRMS (ESI+):** calculated for $C_{20}H_{20}N_2OS$ $(M+H)^+$: 337.7122; found: 337.7148. $[\alpha]_D^{20}$= -47.8 (c= 0.65, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IG-3 column

[CO_2/MeOH (85:15), 120 bar, 40ºC, 3.0 mL/min]: τ_{minor}= 6.44 min, τ_{major}= 8.28 min (95 % *ee*).

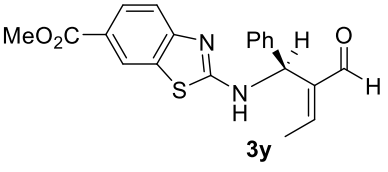
(*S*, *E*)-2-((Benzo[*d*]oxazol-2-ylamino)(phenyl)methyl)but-2-enal (3x)



Following the general procedure described above, compound **3x** was obtained in 73 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.46 – 7.26 (m, 7H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 6.93 (q, *J* = 7.1 Hz, 1H), 6.75 (brd, 1H), 6.26 (brd, 1H), 2.33 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.1, 160.4, 151.7, 147.6, 141.9, 141.3, 138.3, 127.6, 126.6, 125.0, 122.8, 120.0, 115.5, 107.8, 52.2, 14.4. **HRMS (ESI+):** calculated for $C_{18}H_{17}N_2O_2$ $(M+H)^+$: 293.1221; found: 293.1247. $[\alpha]_D^{20}$= -67.10 (c= 0.77, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IB-3 column [CO_2/MeOH (90:10), 120 bar, 40 ºC, 2.0 mL/min]: τ_{major}= 4.15 min τ_{minor}= 4.31 min (87 % *ee*).

Methyl (*S*, *E*)-2-((2-formyl-1-phenylbut-2-en-1-yl)amino)benzo[*d*]thiazole-6-carboxylate (3y)

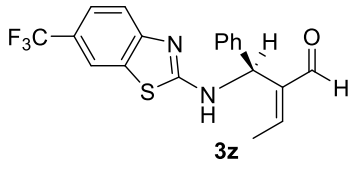


Following the general procedure described above, compound **3y** was obtained in 80% yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.21 (s, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.37 – 7.13 (m, 5H), 6.95 (brd, 1H), 6.82 (q, *J* = 7.1 Hz, 1H), 6.29 (brs, 1H), 3.84 (s, 3H), 2.22 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.0, 167.4, 165.9, 155.2, 152.0, 141.1, 137.9, 129.7, 127.7, 126.7, 126.7, 125.1, 122.5, 121.7, 117.5, 53.5, 50.9, 14.4. **HRMS (ESI+):** calculated for $C_{20}H_{18}N_2O_3SNa$ $(M+Na)^+$: 389.0891; found: 389.0852. $[\alpha]_D^{20}$= -50.9 (c= 0.5, $CHCl_3$). The

enantiomeric excess was determined by SFC using Chiralpak IB-3 column [CO_2/MeOH (90:10), 120 bar, 40 ºC, 2.0 mL/min]: τ_{major}= 9.83 min, τ_{minor} = 11.91 min (>99 % *ee*).

(*S*, *E*)-2-(Phenyl((6-(trifluoromethyl)benzo[*d*]thiazol-2-yl)amino)methyl)but-2-enal (3z)

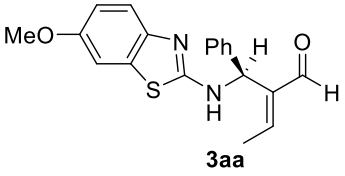


3z

Following the general procedure described above, compound **3z** was obtained in 83% yield as a yellow oil after 24 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.76 (s, 1H), 7.52 - 7.47 (m, *J* = 8.6, 3.4 Hz, 2H), 7.36 – 7.15 (m, 5H), 6.93 (bs, 1H), 6.83 (q, *J* = 7.0 Hz, 1H), 6.27 (bs, 1H), 2.22 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.1, 167.8, 154.9, 153.1, 142.1, 138.9, 130.9, 129.9, 128.7, 127.7, 126.1(q, J_{CF}= 247.3 Hz), 123.1(q, J_{CF}= 25.7 Hz), 119.0 (q, J_{CF}= 7.6 Hz), 118.5, 118.2 (q, J_{CF}= 6.3 Hz), 54.6, 15.5. **HRMS (ESI+):** calculated for $C_{19}H_{15}N_2F_3OSNa$ $(M+Na)^+$: 399.0714; found: 399.0741. $[\alpha]_D^{20}$= -52.3 (c=0.68, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IB-3 column [CO_2/MeOH (90:10), 120 bar, 40 ºC, 2.0 mL/min]: τ_{major}= 3.87 min, τ_{minor} = 4.10 min (>99 % *ee*).

(*S*, *E*)-2-(((6-Methoxybenzo[*d*]thiazol-2-yl)amino)(phenyl)methyl)but-2-enal (3aa)



3aa

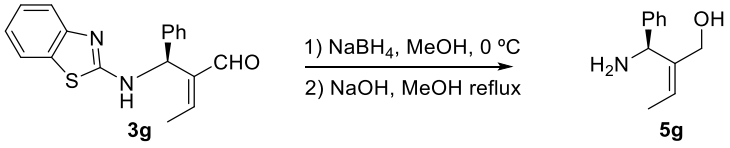
Following the general procedure described above, compound **3aa** was obtained in 85 % yield as a yellow oil after 48 h of reaction. The crude product was purified by flash column chromatography using 3:1 hexane/AcOEt as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.53 (d, *J* = 7.4 Hz, 2H), 7.40 – 7.30 (m, 3H), 7.24 (d, *J* = 7.2 Hz, 2H), 6.89-6.86 (m, 2H), 6.75- 6.73 (m, 2H), 3.73 (s, 3H), 1.56 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 192.4, 156.8, 153.2, 148.1,

146.7, 139.2, 135.9, 135.3, 128.7, 127.9, 127.7, 119.2, 113.7, 108.9, 57.9, 56.1, 14.6. **HRMS (ESI+):** calculated for $C_{19}H_{19}N_2O_2S$ $(M+H)^+$: 339.1102; found: 339.1123. $[\alpha]_D^{20}$= -42.4 (c= 0.82. $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IG-3 column [CO2/MeOH (80:20), 120 bar, 40 ºC, 2.0 mL/min]: τ_{major} = 4.82 min, τ_{minor} = 5.71 min (>99 % *ee*).

4.6.4. Derivatizations

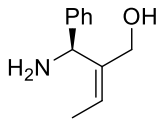
Synthesis of (*S*, *E*)-2-(amino(phenyl)methyl)but-2-en-1-ol (5g)



Scheme 20.

To a solution of aldehyde **3g** (0.1 mmol) in Methanol (2 ml) at 0 ºC, was added $NaBH_4$ in small portions. After consumption (4 hours) of the starting material (followed by TLC). The reaction mixture was added to a separatory funnel with 5 mL of dichloromethane and 5 mL of water. The aqueous phase was extracted with DCM (5 x 5 mL) and the combined organic phases were washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the product quantitatively, which was used in the next step without further purification.

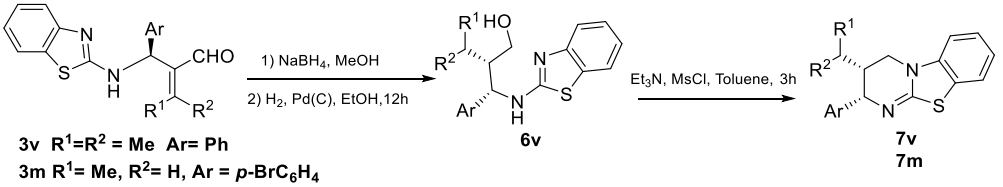
The corresponding alcohol was dissolved in methanol (7 ml) and 5 eq. of NaOH was added. The reaction was heated at reflux overnight. After that time, the reaction mixture was added to a separatory funnel with 5 mL of dichloromethane and 5 mL of water. The aqueous phase was extracted with DCM (5 x 5 mL) and the combined organic phases were washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated to afford the product **5g** without further purification in 61% yield.



5g

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5H), 4.57 (s, 1H), 4.50 (q, *J* = 6.6 Hz, 1H), 3.25 – 3.15 (brd, *J* = 7.9 Hz, 2H), 2.10 (brt, 1H), 1.55 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.1, 135.9, 128.2, 128.0, 127.6, 119.3, 64.4, 56.0, 14.1. **HRMS (ESI+):** calculated for $C_{11}H_{15}NONa$ $(M+Na)^+$: 140.1098; found: 140.1105. $[\alpha]_D^{20}$= -62.3 (c=0.71, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak-IB-3 column [CO_2/MeOH (80:20), 120 bar, 40ºC, 2.0 mL/min]: τ_{major} = 7.52 min, τ_{minor} = 8.24 min. (94 % *ee*).

Synthesis of (2*S*, 3*R*)-3-alkyl-2-aryl-3,4-dihydro-2*H*-benzo [4,5]thiazolo[3,2-*a*]pyrimidine (7v and 7m)



3v R^1=R^2 = Me Ar= Ph
3m R^1= Me, R^2= H, Ar = *p*-BrC$_6$H$_4$

6v

7v
7m

Scheme 21.

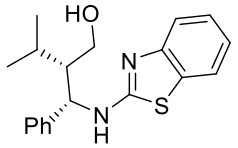
To a solution of aldehyde **3v** or **3m** (0.2 mmol) in Methanol (2 ml) at 0 ºC, was added $NaBH_4$ (3 eq.) in small portions. After consumption (5 hours) of the starting material (followed by TLC). The reaction mixture was added to a separatory funnel with 5 mL of dichloromethane and 5 mL of water. The aqueous phase was extracted with DCM (5 x 5 mL) and the combined organic phases were washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated to afford the product quantitatively, which was used without further purification.

The corresponding alcohol was dissolved in ethanol (2 ml). 10% of Pd\C was added and the solution was stirred under H_2 pressure (balloon) for 12 hours at 40 ºC. Once completed, the crude was purified via column chromatography (Hexane/ AcOEt 1:1) to afford the desire product as a white solid (60 % yield **6v**, 65% yield **6m**).

Finally, to a solution of **6v** or **6m** and Et_3N (3.06 eq.) in anhydrous CH_2Cl_2 (3 ml) at 5 ºC under argon was added methanesulfonylchloride (1.53 eq.) over 10 mins and the solution allowed to r.t. The solution was stirred for 1.5 h at which time NMR

spectroscopic analysis indicated the consumption of alcohol. Then methanol was added followed by Et_3N and the solution heated to reflux for 1.5 h at which time NMR spectroscopic indicated the formation of **7v**. The crude was purified via column chromatography (Hexane/ AcOEt 3:1) to afford the desire product as a white solid (55 % yield **6v**, 61% yield **6m**).

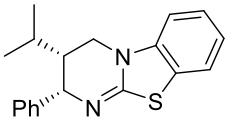
(*S*)-2-((*S*)-(Benzo [*d*]thiazol-2-ylamino)(phenyl)methyl)-3-methylbutan-1-ol (6v)



6v

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 - 7.54 (m, 3H), 7.46 (app d, *J* = 8.1 Hz, 1H), 7.40 - 7.25 (m, 4H), 7.10 - 7.04 (m, 1H), 4.96 (d, *J* = 3.7 Hz, 1H), 3.96 (dd, *J* =10.5, 3.8 Hz, 1H), 3.71 (t, *J* = 10.2 Hz, 1H), 2.18-2.24 (m, 1H), 1.66-1.73 (m, 1H), 1.52 (brs, 1H), 1.15 (d, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.3, 151.4, 138.9, 129.1, 128.3, 128.1, 127.5, 125.9, 121.0, 120.9, 118.1, 62.3, 60.2, 50.7, 26.7, 22.6, 19.6. **HRMS (ESI+):** calculated for $C_{19}H_{22}N_2OS$ $(M+Na)^+$: 349.1498; found: 349.1477. $[\alpha]_D^{20}$= -53.7 (c=0.5, $CHCl_3$).

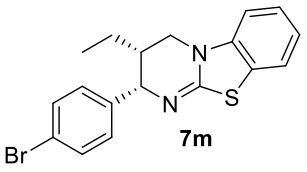
(2*S*, 3*R*)-3-Isopropyl-2-phenyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine (7v)



7v

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 - 7.23 (m, 7H), 7.07 (td, *J* = 7.6, 1.3 Hz, 1H), 6.85 (d, *J* = 7.7 Hz 1H), 4.96 (dd, *J* = 4.7, 1.3 Hz, 1H), 3.92 (ddd, *J* = 11.2, 4.9, 1.5 Hz, 1H) 3.39 (app. t, *J* = 11.3 Hz, 1H), 1.94-2.04 (m, 1H), 1.29-1.41 (m, 1H), 1.17 (d, J = 6.5 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.3, 140.6, 140.5, 128.3, 128.1, 127.2, 125.9, 123.1, 122.0, 121.8, 107.5, 61.3, 41.9, 40.9, 26.9, 22.0, 20.0. **HRMS (ESI+):** calculated for $C_{19}H_{20}N_2S$ $(M+Na)^+$: 331.1248; found: 331.1224. $[\alpha]_D^{20}$= +279.8 (c=0.5, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IA column [CO_2/MeOH (90:10), 120 bar, 40 ºC, 1.0 mL/min]: τ_{major} = 20.85 min, τ_{minor} = 23.41 min. (93% *ee*).

(2*S*, 3*R*)-2-(4-Bromophenyl)-3-ethyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine (7m)



7m

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.32 - 7.27 (m, 3H), 7.17 – 7.12 (m, 1H), 7.01 - 6.90 (m, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 5.43 (d, *J* = 3.1 Hz, 1H), 3.91 (dd, *J* = 12.4, 2.6 Hz, 1H), 3.67 (app. t, *J* = 12.5, 1H), 2.87 (m, 1H), 1.73 (m, 1H), 1.66 (m, 1H), 0.99 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.7, 140.3, 135.7, 132.0, 131.8, 128.1, 127.8, 127.6, 124.6, 121.6, 112.5, 58.4, 46.6, 39.8, 25.2, 12.0. **HRMS (ESI+):** calculated for $C_{18}H_{17}BrN_2SNa$ $(M+Na)^+$: 395.0258; found: 395.0241. $[\alpha]_D^{20}$= +252.3 (c= 0.65, $CHCl_3$). The enantiomeric excess was determined by SFC using Chiralpak IB-3 column [CO_2/MeOH (80:20), 120 bar, 40ºC, 2.0 mL/min]: τ_{major} = 5.82 min, τ_{minor} = 6.49 min. (95 % *ee*).

CONCLUSIONES GENERALES

Conclusiones Generales

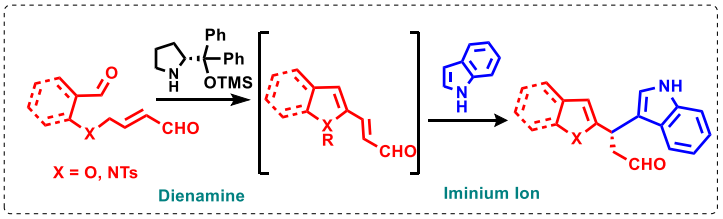
En la presente tesis, se han descrito nuevas metodologías para el desarrollo de nuevas reacciones asimétricas, empleando tanto catalizadores monofuncionales como bifuncionales quirales, con el fin de obtener diversos compuestos de interés farmacéutico e industrial.

En el primer capítulo se empieza con una pequeña introducción de Organocatalisis, área en la que esta englobada esta tesis doctoral. Los organocatalizadores presentan dos funciones importantes, pueden activar o bien al electrófilo o al nucleofilo (catalizadores monofuncionales) o bien a los dos a la vez (catálisis bifuncional). Además los organocatalizadores pueden clasificarse en función del modo de acción. En catálisis covalente, se produce un enlace covalente entre el sustrato y el catalizador. Este tipo de catálisis es la que se ha llevado a cabo en el objetivo del capítulo 1. Por otro lado en la catálisis no covalente, la activación del sustrato se lleva a cabo a través de un enlace de hidrogeno, como en el caso de los catalizadores bifuncionales empleados en los capítulos 3 y 4.

Se continúa el primer capítulo con una introducción más profunda de la aminocatálisis. Gracias a la experiencia de mi grupo en este tipo de catálisis, hemos podido desarrollar una reacción “one pot” basada en la química de dienamina e ion iminio, para poder llevar a cabo la síntesis de diheteroarylalcanales enantiomericamente enriquecidos. Estos productos son compuestos naturales de tremenda importancia biológica, ya que presentan propiedades antitumorales y analgésicas entre otras.

Se pudo comprobar que la reacción es compatible con un gran número de sustituyentes en las diferentes posiciones de los productos de interés, todos ellos obtenidos con buenos rendimientos y excelentes excesos enantiomericos. Debido a que compuestos similares descritos en la bibliografía presentaban actividad antitumoral frente a distintos tipos de cáncer, decidimos llevar a cabo el análisis antiproliferativo de los nuevos compuestos en cuatro líneas tumorales distintas. La relación estructura-actividad de los compuestos revelaron que ciertos compuestos con determinada sustitución pueden llegar a ser tan citotóxicos como el CDDP,

antitumoral por excelencia en clínica actualmente. Por ejemplo, en el caso del compuesto 5af en la línea tumoral WiDr (cáncer de colon), la actividad antiproliferativa fue superior incluso que el CDDP.



Esquema 1. Objetivo del primer capítulo.

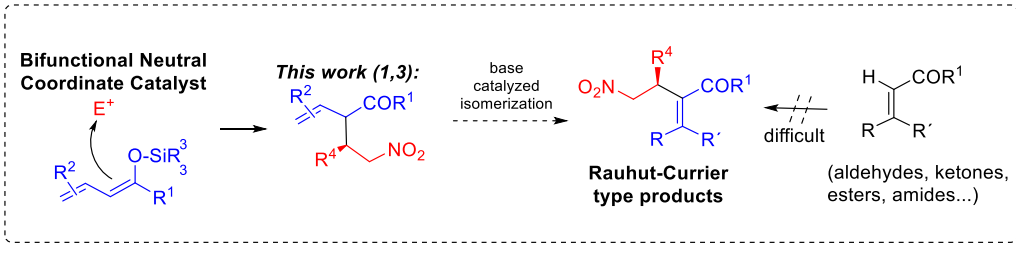
En el segundo capítulo se lleva a cabo una recopilación de los distintos modos de activación de la reacción asimétrica de Mukaiyama vinilóga. Se comienza con una introducción a la importancia de la reacción clásica de Mukaiyama y las ventajas que aporta frente a la reacción aldólica. Dicho capitulo está dividido en diferentes apartados según los distintos tipos de catalizadores empleados en cada reacción, así como las ventajas e inconvenientes de cada activación catalítica. También se pone de manifiesto la importante aplicabilidad de esta reacción en la síntesis de diversos productos naturales.

De todo lo que aprendimos escribiendo el review que da título al segundo capítulo, nos propusimos como objetivos el estudio de la activacion de silil-dienol éteres con diferentes electrófilos, empleando la catálisis bifuncional. De esta manera surgieron los capítulos 3 (Desarrollo de la reacción Mukaiyama-Michael viniloga en presencia de nitroalquenos) y del capítulo 4 (Estudio de la reacción de Mukaiyama Mannich viniloga, empleando iminas como electrófilos).

En el capítulo 3, y de forma inesperada hemos observado que los catalizadores bifuncionales son capaces de cambiar la reactividad y regioselectividad de los dienolatos de silicio. Esto provoca un cambio dramático en la regioselectividad de 1,5 a la funcionalización 1,3. Este hecho ha permitido por primera vez la adición 1,3 de nitroalquenos a silil-dienol éteres, permitiendo la síntesis de dobles enlaces tri- y tetra sustituidos en los productos finales de Ruahut-Currier.

La metodología descrita permite el uso de una gran variedad tanto de nitroalquenos como de dienolatos de silicio, para dar lugar a los productos Rauhut-Currier que albergan en su estructura aldehídos, esteres, cetonas y amidas, los cuales no son posible de obtener por ningún otro tipo de método.

La reacción se lleva a cabo bajo condiciones suaves y con altos rendimientos y excesos enantioméricos. Además hemos propuesto un modelo mecanistico basado en hechos experimentales y cálculos teóricos, que ponen de manifiesto que la etapa limitante de la reacción es la hidrolisis del silil-dienol éter, seguida de la formación del enlace C-C de una forma enantio y regioselectiva, resultado de la orientación apropiada de los sustratos y el catalizador bifuncional en el correspondiente estado de transición.



Esquema 2. Resultados obtenidos del capítulo 3.

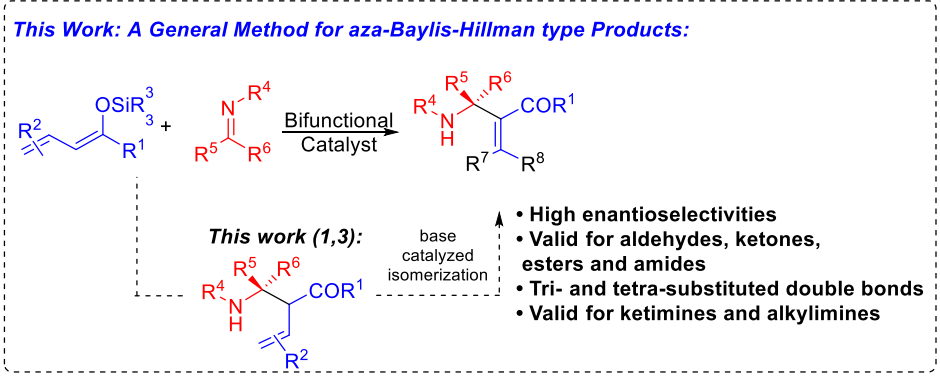
En último lugar, en el capítulo 4, hemos desarrollado una nueva estrategia para la síntesis de productos tipo aza-Baylis-Hillman, a través de una reacción formal Mukaiyama Mannich viniloga.

En este caso, se emplean iminas como electrófilos y al igual que en el capítulo anterior, solo se observó exclusivamente la regioselectividad 1,3. Tras una larga optimización de diferentes iminas, encontramos la imina de benzotiazol, con la que conseguimos excesos enantioméricos por encima del 99%.

Este hecho nos permitió desarrollar un método general para la obtención de productos aza-Baylis-Hillman, incluyendo los productos tri- y tetra sustituidos, muy difíciles de obtener por los métodos convencionales.

Además, fáciles derivatizaciones de los productos finales conducen a intermedios muy importantes en síntesis orgánica como son los 1,3 aminoalcoholes o los catalizadores tipo base de Lewis.

Por último, se ha propuesto un modelo mecanístico basado en los hechos experimentales observados.



Esquema 3. Metodología desarrollada en el capítulo 4.